

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206439Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206439

SUPPL #

HFD # 120

Trade Name Namzarcic

Generic Name memantine HCl ER / donepezil

Applicant Name Forest Laboratories

Approval Date, If Known December 23, 2014

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor provided two studies, a bioequivalence study, MD-PK-104, and a bioavailability study, MDX-PK-105, for review. These studies are described by the sponsor as a bioequivalence study and a bioavailability study, respectively.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES X NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES X      NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#                      Memantine hydrochloride ER

NDA#                      Aricept (donepezil)

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

## **PART III      THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO X

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?



(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Teresa Wheelous, R. Ph.  
Title: Sr. Regulatory Project Manager  
Date: April 3, 2015

Name of Office/Division Director signing form: Billy Dunn, MD  
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

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TERESA A WHEELOUS

04/03/2015

WILLIAM H Dunn

04/03/2015

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 206439		
Proprietary Name: Namzaric Established/Proper Name: memantine HCl ER / donepezil Dosage Form: Capsule		Applicant: Forest Laboratories Agent for Applicant (if applicable): Kathleen Waldron
RPM: Teresa Wheelous, R. Ph.		Division: Neurology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)                             <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)</li> </ul> </li> </ul> Date of check: 10/28/14  <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	

Actions <ul style="list-style-type: none"> <li>• Proposed action 12/26/14</li> <li>• User Fee Goal Date is 12/26/14</li> <li>• Previous actions (specify type and date for each action taken)</li> </ul>	X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain	<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority

Chemical classification (new NDAs only):

*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	X No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

<b>Action Letters</b>	
A Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval 12/23/14
<b>Labeling</b>	
B Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> <li>Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 12-18-14</li> </ul>	X Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	X Included
C Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 12/18/14</li> </ul>	X Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
D Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	X Included
E Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (indicate date(s))</li> <li>Review(s) (indicate date(s))</li> </ul>	5/23/14 5/19/14
F Labeling reviews (indicate dates of reviews) DMEPA – 10/01/14, DMPP 12/16/14, OPDP 12/16/14	RPM: X None DMEPA: X None DMPP/PLT (DRISK): X None OPDP: X None SEALD: <input type="checkbox"/> None ✓ CSS: <input type="checkbox"/> None ✓ Other: <input type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
G RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	4/15/14
H All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee Cleared -11/13/14	<input type="checkbox"/> Not a (b)(2)
I NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
J Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<b>K Pediatrics (approvals only)</b> <ul style="list-style-type: none"> <li>• Date reviewed by PeRC: <u>12/03/2013</u></li> <li>If PeRC review not necessary, explain: _____</li> </ul>	
<b>L Outgoing communications:</b> letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	
<b>M Internal documents:</b> memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
<b>N Minutes of Meetings</b>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting <b>IND 109763</b></li> </ul>	<input type="checkbox"/> No mtg 11/19/13
<ul style="list-style-type: none"> <li>• EOP2 meeting <b>IND 109763</b></li> </ul>	<input type="checkbox"/> No mtg 10/13/11
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• _____</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings- Type C Meeting <b>IND 109763 6/20/13</b></li> </ul>	
<b>❖ Advisory Committee Meeting(s)</b>	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<b>O Office Director Decisional Memo</b> ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/23/14
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
<b>P Clinical Reviews</b>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) – N/A</li> </ul>	<input type="checkbox"/> No separate review 12/19/14
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>) 12/19/14</li> </ul>	12/19/14
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<b>Q Financial Disclosure reviews(s) or location/date if addressed in another review</b> OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

<b>Risk Management</b> <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>		✓ None
<b>R</b> OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> ) BIOEQUIVALENCE 11/10/14		None requested
<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
<b>Biostatistics</b>		<input type="checkbox"/> None
<b>S</b> Statistical Division Director Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> ) 10-27-14		<input type="checkbox"/> None 10/27/14
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
<b>T</b> Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> ) 11-16-14		<input type="checkbox"/> None 11/16/14
OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )		<input type="checkbox"/> None requested
<b>Nonclinical</b>		<input type="checkbox"/> None
<b>U</b> Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> ) 11-23-14		<input type="checkbox"/> No separate review 11/23/14
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> ) 10-25-14		<input type="checkbox"/> None 10/25/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )		<input type="checkbox"/> None requested

Product Quality	<input type="checkbox"/> None
V Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 9/24/14, 10/26/14, 11/21/14
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
✓ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites <sup>5</sup> )	Date completed: ✓ Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

**Day of Approval Activities**

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	X No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

**PeRC PREA Subcommittee Meeting Minutes  
December 3, 2014**

**PeRC Members Attending:**

Wiley Chambers

George Greeley

Kevin Krudys

Dionna Green

Dianne Murphy

Kristiana Brugger

Colleen LoCicero

Julia Pinto

Greg Reaman (b) (4) review only)

Hari Cheryl Sachs

Michelle Roth-Cline

Karen Davis-Bruno

Peter Starke

Olivia Ziolkowski

Rosemary Addy

Barbara Buch

Nisha Jain (b) (4) review only)

Adrienne Hornatko-Munoz (b) (4) only)

**PREA**



(b) (4)

<i>NDA</i>	<i>206439</i>	<i>Namzaric (Full Waiver)</i>	<i>The treatment of moderate to severe dementia of the Alzheimer's type.</i>
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(b) (4)



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

**Namzaric (memantine HCL/donepezil) Full Waiver**

- Proposed Indication: The treatment of moderate to severe dementia of the Alzheimer's type.
- This application triggers PREA as a new active ingredient.
- The PDUFA goal date is December 26, 2014.
- *PeRC Recommendations:*
  - The PeRC agreed with the Division to grant a full waiver because the disease/condition does not exist in children.



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/s/  
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GEORGE E GREELEY  
12/22/2014



NDA 206439

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Kathleen Waldron, MBA, Senior Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Ms. Waldron:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Memantine Hydrochloride Extended Release/Donepezil Hydrochloride Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Your proposed dissolution acceptance criteria for Memantine HCl/Donepezil HCl Capsules are neither supported by the data nor adequately justified; they are therefore not acceptable. In particular, the IVIVC model established for the single-entity memantine product, Namenda XR, in NDA 22525 does not support the dissolution acceptance criteria that you have proposed for the memantine component of the FDC product. We have recommended different dissolution acceptance criteria for memantine in the FDC product on the basis of the following:

- i) The (b)(4) dissolution rate of the biobatch (Lot # 23559) relative to the clinical batch in NDA 22525; we note that the change in the (b)(4) (in 2013) may have contributed, at least in part, to the (b)(4) dissolution rate observed in the FDC product; and
- ii) Batch release and long-term stability dissolution data for the biobatch and registration batches.

The dissolution method and FDA-recommended dissolution acceptance criteria for your proposed FDC product are as follows:

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criteria										
1 (basket)	100 rpm	900 ml of NaCl/HCl buffer, pH 1.2 at 37 ± 0.5 °C	<b>Donepezil:</b> Q = (b)(4)% at 15 min										
			<b>Memantine:</b>										
			<table border="1"> <thead> <tr> <th>Time (hours)</th> <th>Acceptance Limits</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>NMT (b)(4)%</td> </tr> <tr> <td>4</td> <td>(b)(4)%</td> </tr> <tr> <td>8</td> <td>(b)(4)%</td> </tr> <tr> <td>12</td> <td>NLT (b)(4)%</td> </tr> </tbody> </table>	Time (hours)	Acceptance Limits	1	NMT (b)(4)%	4	(b)(4)%	8	(b)(4)%	12	NLT (b)(4)%
			Time (hours)	Acceptance Limits									
			1	NMT (b)(4)%									
4	(b)(4)%												
8	(b)(4)%												
12	NLT (b)(4)%												

Provide a revised Drug Product Specifications Table and amend the Drug Product Stability Protocol accordingly.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

**Olen Stephens -A**

Digitally signed by Olen Stephens -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -A,  
0.9.2342.19200300.100.1.1=200055826  
Date: 2014.10.31 10:56:38 -04'00'

Olen Stephens, Ph.D.  
Acting Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

## Wheelous, Teresa A

---

**From:** Shah, Vibhakar J  
**Sent:** Tuesday, July 22, 2014 4:55 PM  
**To:** Martin, Jewell; Bouie, Teshara; Wheelous, Teresa A  
**Cc:** Chu, Pei-I; Eradiri, Okpo; Dorantes, Angelica; Heimann, Martha R; Stephens, Olen; CDER OMPQ REVIEW; Ramanadham, Mahesh  
**Subject:** NDA 206439 - Facility Inspection/Compliance Status update - July 22, 2014  
**Attachments:** N206439EES\_SummaryReport22Jul2014Fnl.pdf  
**Importance:** High

Hi Jewell, Teshara and Teresa,

Please note that an overall **ACCEPTABLE** recommendation was made on May 30, 2014 by OC/OMPQ for all the manufacturing/testing facilities that are listed in the EES in support of the **NDA 206439 for Memantine HCl extended release/ Donepezil HCl capsules**. Please refer to the attached PDF copy of the final EES summary report. A system generated message may be forthcoming.

Feel free to contact me, if you have a question/comment or need clarification in this regard.

Thanks,

*- Vibhakar*

**Vibhakar Shah, Ph.D.**

*Senior Policy Advisor*

DGMPA/OMPQ/OC/CDER/USFDA

**Phone:** 301-796-1750; **Fax:** 301-847-8741

**Email:** [vibhakar.shah@fda.hhs.gov](mailto:vibhakar.shah@fda.hhs.gov)

**p.s.:** Please excuse any typos

---

**From:** Stephens, Olen  
**Sent:** Tuesday, July 22, 2014 3:19 PM  
**To:** Martin, Jewell; Heimann, Martha R; Eradiri, Okpo; Chu, Pei-I; Shah, Vibhakar J  
**Cc:** Dorantes, Angelica; Bouie, Teshara  
**Subject:** RE: NDA 206439 Quality Midcycle Mtg (if needed)

I'd like to hold the meeting even if it is a short one. I know that Pei-I has sent out an IR, but want to hear where we are with the other reviewers.

Thanks,

Olen

*Olen Stephens  
Acting Branch Chief  
Branch 1, Division 1  
ONDQA*

---

**From:** Martin, Jewell  
**Sent:** Tuesday, July 22, 2014 3:16 PM  
**To:** Stephens, Olen; Heimann, Martha R; Eradiri, Okpo; Chu, Pei-I; Shah; Vibhakar J  
**Cc:** Dorantes, Angelica; Bouie, Teshara  
**Subject:** RE: NDA 206439 Quality Midcycle Mtg (if needed)

Hello,

I am covering for Teshara. She told me that this meeting was tentatively scheduled. Please let me if the meeting is still required.

Thanks,

Jewell

-----Original Appointment-----

**From:** Bouie, Teshara  
**Sent:** Thursday, July 17, 2014 3:48 PM  
**To:** Bouie, Teshara; Stephens, Olen; Heimann, Martha R; Eradiri, Okpo; Chu, Pei-I; Shah, Vibhakar J; Martin, Jewell  
**Cc:** Dorantes, Angelica  
**Subject:** NDA 206439 Quality Midcycle Mtg (if needed)  
**When:** Wednesday, July 23, 2014 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).  
**Where:** CDER WO 2560 conf rm Bldg21

Call-in #:

(b) (4)

Passcode: (b) (4)



NDA 206439

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Kathleen Waldron, MBA, Senior Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Ms. Waldron:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Memantine Hydrochloride Extended Release/Donepezil Hydrochloride Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide justification for why an (b)(4)% assay limit for the memantine (b)(4) was selected. For example at the lower end of your assay limit, are there (b)(4) considerations for the (b)(4) process? Would an (b)(4)% assay limit allow you to (b)(4) that meet the memantine assay specification, ensuring efficacy for the patient?
2. Include residual solvent testing in the drug product specifications and propose a limit for this specification. Alternatively, provide justification for why residual solvents are not monitored and how your current control strategy for residual solvents does not adversely impact patient safety.
3. Your proposed total impurity limit (b)(4) for donepezil HCl is higher than the USP limit of 0.75% - 1% for donepezil product. Lower the total impurity limit to (b)(4)% to be consistent with the USP recommendation. Alternatively, provide justification for why (b)(4)% is acceptable from a patient safety perspective.
4. Provide the moisture vapor transmission rate per tablet for the container closures used in the registration stability study and the commercial product to demonstrate that the different container closure systems do not impact product quality.
5. Your proposal to calculate the expiration date of the commercial product based on the (b)(4) date of the donepezil HCl (b)(4) batches is not acceptable. The expiration

date of your product should be based on the date of production. The date of production is the date that the first step of manufacture is performed (b) (4) in the production of a dosage form.

6. Request and submit updated letters of authorization (LOA) that provide the most updated name, reference number, volume, and page number for DMF (b) (4), DMF (b) (4) and DMF (b) (4) per 21CFR314.420(b) to facilitate our review of these DMF's.
7. Provide a list of analytical tests performed and acceptance criteria for receiving the donepezil drug substance at the drug product manufacturing site.
8. Please provide your most recent stability data for the registration batches of your drug product.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Acting Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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OLEN M STEPHENS  
07/11/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993

NDA 206439

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Forest Laboratories, Inc.  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

ATTENTION: Kerri Kaplan, PharmD  
Senior Manager, Regulatory Affairs

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated and received February 26, 2014, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Memantine HCl Extended Release/Donepezil HCl Capsules, 14/10 mg and 28/10 mg.

We also refer to your correspondence, dated and received February 27, 2014, requesting review of your proposed proprietary name, Namzaric.

We have completed our review of the proposed proprietary name, Namzaric and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your February 27, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Teresa Wheelous, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
05/23/2014



NDA 206439

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Forest Laboratories, Inc.  
Attention: Kerri Kaplan, PharmD  
Senior Manager, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Kaplan:

Please refer to your New Drug Application (NDA) dated and received February 26, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for TRADENAME (memantine HCl extended release / donepezil HCl) Capsules 14mg /10mg and 28mg /10mg.

We also refer to your amendment dated February 27, 2014, which provides a proprietary name review request.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 27, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

### CMC

1. Submit a comprehensive regulatory acceptance specification for Donepezil Hydrochloride (i.e., test parameters, analytical procedures, and acceptance criteria) to the NDA. The specification should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt, or periodically for vendor requalification. You may incorporate USP compendial methods by reference; however, you should provide information to support suitability of the methods to the bulk material supplied by (b) (4) (e.g., for determination of process impurities). Provide all other analytical procedures and supporting method validation data in the application.
2. Per 21 CFR 314.54(a)(1)(i), submit the master batch records for commercial manufacture (including packaging) of each strength of the drug product.

### BIOPHARMACEUTICS

1. In order for the previously established IVIVC model with the single-entity Memantine ER product to be applicable to your proposed FDC capsule, memantine's dissolution acceptance criteria must be the same as the dissolution criteria approved under NDA 22525 for Namenda XR. Therefore, implement these acceptance criteria for the memantine component of your proposed FDC donepezil/memantine product and provide the revised Specifications Table for the drug product reflecting these changes:

1 h	(b) (4)	
4 h		%
8 h		%
12 h		

2. Please provide Summary Tables for the bioanalytical method validation and its performance in study # MDX-PK-104 using the following template.

### Bio-Analytical Method Report Summary In-Study Validation

Matrix	
Sample Volume Required, Storage Conditions, Extraction Procedure	
Concentration Range	
Analytical Methodology	
Detection	
Regression Type	
Coefficient of Determination	

Between-Batch Accuracy	standards QCs	
Between-Batch CV	standards QCs	
Within-Batch	Accuracy CV	
Recovery	Drug Reference	
Stability in human plasma	Room temp Freeze/thaw Long term	
Solution Stability	at room temp at 4°C	
Reference Solution Stability	at room temp at 4°C	
LLOQ (Accuracy / CV)		
Processed Stability	at 4°C	
Dilution Integrity (v:v sample-blank)		

### **PROPRIETARY NAME REVIEW**

Please provide a blister pack sample for our review.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. 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)]. We found the following:
  - a. 2.1 "G" (Guidelines) needs capitalized;
  - b. 7.2 "O" (Other) needs capitalized.
2. 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)]”. We found the following:
  - a. In 8.6, 8.7 and 12.3, cross reference for Dosage and Administration should state 2.2, not 2.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 30, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Division Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ERIC P BASTINGS  
05/09/2014



NDA 206439

**NDA ACKNOWLEDGMENT**

Forest Laboratories, Inc.  
Attention: Kerri Kaplan, PharmD  
Senior Manager, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Kaplan:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TRADENAME (memantine HCl extended release / donepezil HCl)  
Capsules 14mg /10mg and 28mg /10mg

Date of Application: February 26, 2014

Date of Receipt: February 26, 2014

Our Reference Number: NDA 206439

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 27, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 206439** submitted on February 26, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neurology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Teresa Wheelous, R. Ph.  
Sr. Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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TERESA A WHEELOUS  
03/25/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 109763

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Kerri Kaplan, PharmD  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Kaplan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MDX-8704 (memantine HCL extended release and donepezil HCL) fixed dose combination.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss the sufficiency of studies to be included in an NDA to permit the review and potential approval of MDX-8704 for the treatment of moderate to severe dementia of the Alzheimer's type in patients who are already being treated with the combination of memantine and donepezil.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 19, 2013 3 PM  
**Meeting Location:** White Oak Bldg. 22, Conference room 1311

**Application Number:** 109763  
**Product Name:** Memantine HCl ER / donepezil  
**Indication:** Alzheimer's Disease

**Sponsor/Applicant Name:** Forest Research Institute Inc.

**FDA ATTENDEES (tentative)**

Eric Bastings, MD – Acting Director, Division of Neurology Products  
Nicholas Kozauer, MD – Clinical Team Leader  
Ranjit Mani, MD – Clinical Reviewer  
Xinning Yang, PhD – Clinical Pharmacology Reviewer  
Martha Heimann, PhD – CMC Team Leader  
Okpo Eradiri, Ph.D. - Biopharmaceutics Reviewer  
Pei-I Chu, PhD – CMC Reviewer  
Jacqueline Sheppard – DMEPA Reviewer  
Ermas Zerislassie - DMEPA Project Manager – via telephone  
Charlene Flowers – OSE Safety Reviewer  
Neshiewat, Julie – DMEPA Team Leader  
Teresa Wheelous – Sr. Regulatory Project Manager, Division of Neurology Products

**FOREST RESEARCH INSTITUTE ATTENDEES**

June Bray, R. Ph., M.B.A. - Senior Vice President, Regulatory Affairs  
Kerri Kaplan, PharmD. - Senior Manager, Regulatory Affairs  
Natalie McClure, Ph.D. - Senior Vice President, Product Development, Adamas Pharmaceuticals, Inc.  
Alexander Bischoff, Ph.D. - Director, Regulatory Affairs CMC  
Andreas Grill, M.B.A. - Executive Director, Pharmaceutical R&D  
Ramesh Boinpally, Ph.D. - Fellow, Clinical Pharmacology Drug Dynamics

**BACKGROUND**

[The background section should contain the following information to set a context for the meeting:

- (i) Purpose of meeting.
- (ii) Names of drug (include established/generic/proper name); pharmacologic class; mechanism of action, if known.
- (iii) If the product is a 505(b)(2), explain how it is different from the listed drug to be relied upon for approval. Or, explain that only literature will be relied upon.
- (iv) A brief history of events leading up to this meeting, including but not limited to previous decisions and actions.
- (v) Context for product development. Include a brief description of any protocols to be discussed at the meeting and not just a reference to the description of the protocol in the briefing package or previous meeting minutes.
- (vi) Expected outcome for the meeting]

**DISCUSSION QUESTIONS**

1. **As the NDA will contain only bioequivalence/bioavailability studies, does the Division concur that an Integrated Summary of Safety/Integrated Summary of Effectiveness and Summary of Clinical Safety/Summary of Clinical Efficacy are not necessary?**

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

2. **If so, does the Division agree that the Clinical Overview in Module 2.5 can be utilized to summarize relevant information regarding the studies included in the NDA and to indicate our intention to rely on the Agency's previous findings of safety and effectiveness for the listed drug Aricept<sup>®</sup>, as well as to reference relevant information from the Namenda<sup>®</sup> and Namenda XR<sup>®</sup> NDAs?**

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

- 3. Given that bioequivalence between the FDC (28/10 mg) and the free components (Study MDX-PK-104) and lack of food effect for the FDC (28/10 mg) (Study MDX-PK-105) have been demonstrated, does the Division agree that the data from these studies are adequate to support the NDA filing and potential approval of MDX-8704 for patients who are already being treated with the combination of memantine and donepezil?**

**Preliminary Meeting Comments:**

You should provide information about the alcohol dumping effect of your product; an *in vitro* study should suffice for that purpose, at least as a first step. An *in vitro* study of Namenda® XR submitted as part of the NDA for that product found some evidence of dumping at alcohol concentrations of 20% and 40%. Please also refer to the minutes of the End-of-Phase 2 meeting held on October 13, 2011 for our earlier comments about the same subject.

**Meeting Discussion:**

The sponsor acknowledged that in-vitro alcohol dose-dumping would be investigated for MDX-8704: if that investigation yielded results similar to those for Namenda XR were obtained, the clinical relevance of those results would also be judged similarly. The Agency agreed with that proposal.

- 4. Does the Division concur with the submission of case report forms and narratives only for subjects who discontinued due to an adverse event (AE) or experienced a serious adverse event (SAE), including death, from these 2 bioequivalence/bioavailability studies?**

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

- 5. Does the Division agree that the data and justification provided in the briefing package support the granting of a biowaiver request for the 14/10 mg dosage strength?**

**Preliminary Meeting Comments:**

The intended content of your biowaiver request package appears reasonable. As we informed you during the Type C meeting held on June 20, 2013, the percentage (w/w) composition of each component in a fixed-dose combination dosage form should be calculated on the basis of total unit weight, not on the weight of separate (b) (4), or some other intermediate forms. However, your supporting data for the biowaiver request may obviate the

need for demonstration of compositional proportionality of the high and low strengths of your proposed combination product.

We agree with the use of the established *in vivo-in vitro* correlation (IVIVC model) for the memantine extended-release component of your product. Please use the established IVIVC model to predict the memantine pharmacokinetic profile (AUC and  $C_{max}$ ) based on the *in vitro* dissolution data. For the immediate-release component of your product, donepezil, comparative dissolution data in 3 different dissolution media will be acceptable if a Biopharmaceutics Classification System (BCS) (b) (4) designation is granted by FDA's BCS Committee.

We acknowledge receipt of your submission to the BCS Committee requesting BCS (b) (4) designation for donepezil in your proposed fixed-dose combination capsule.

#### Meeting Discussion:

The sponsor's understanding of the requirements for obtaining a biowaiver for the 14/10 mg dosage strength of MDX-8704 was outlined. The Agency concurred that the sponsor's understanding of that matter was consistent with the preliminary comments provided in response to this question. The sponsor asked if the Agency could provide assurance that the BCS Committee was likely to finalize its decision regarding the sponsor's biowaiver request and communicate that decision to the sponsor prior to the proposed filing of the NDA for MDX-8704 in February 2014. The Agency stated that although the average time for evaluating BCS submissions was 3 to 4 months, a firm assurance could not be provided as to how quickly the sponsor's biowaiver request might be reviewed, as the time that the Agency might require for that purpose would depend on the resources available and other related factors.

6. ~~Does the Division concur that the comparability protocol included in this briefing package is sufficient to demonstrate equivalence between batches manufactured at the clinical manufacturing site and at the commercial manufacturing site?~~

#### Preliminary Meeting Comments:

##### Chemistry

Please refer to the minutes of the Type C meeting that was held on June 20, 2013.

You should provide information on the equipment used for (b) (4) and demonstrate that the products are of the same quality and meet the same specification. In this particular instance, stability data from the clinical manufacturing site can be used to support the product shelf life. You should provide release data including dissolution profiles of the three batches made at the commercial site at the time of filing of the NDA. The first three commercial batches should be placed on both accelerated and long term stability.

Thereafter, one batch per year should be placed on stability. The adequacy of the data provided will be evaluated during review of the NDA.

### Biopharmaceutics

As we stated at the Type C meeting held on June 20, 2013, the site change you have proposed for [REDACTED] <sup>(b) (4)</sup> final steps in the manufacturing process, is a Scale-Up and Post-Approval Changes Modified-Release (SUPAC-MR) [REDACTED] <sup>(b) (4)</sup> change that requires a bridging bioequivalence study. However, you have an approved IVIVC model that could be used to support the approval of the commercial site. The following information would then be needed:

For the memantine extended-release component of your product:

- Please use the IVIVC model approved by the Agency for memantine to predict systemic exposure ( $C_{max}$ , AUC) based on the dissolution profiles. The differences in the predicted  $C_{max}$  and AUC between the two manufacturing sites should not be more than the 20% allowable maximum difference.
- The complete *in vitro* dissolution profile data and the *in vivo* generated pharmacokinetic data should be provided

For the donepezil immediate-release component of your product:

- Please provide the multipoint comparative dissolution and  $f_2$  data in 3 different pH-media.

Please revise the comparability protocol as appropriate to include the submission of this information.

### Meeting Discussion:

The sponsor summarized the type of data pertinent to this item of discussion that would be included in the planned NDA submission; the Agency concurred with that proposal.

- 7. As proposed at the Type C FDA meeting on 20 Jun 2013, Forest plans to submit 6-month accelerated and 6-month long-term stability data in the original NDA submission, and will amend the NDA to include the 9-month long-term stability data within 30 days of the submission of the original NDA.**
  - a. Does the Division agree that the NDA can be amended with 9-month long-term stability data within 30 days of the submission of the original NDA?**
  - b. Does the Division agree that the proposed stability package is sufficient to permit approval of an 18-month shelf life?**

**Preliminary Meeting Comments:**

Please refer to the Minutes of the Type C meeting that was held on June 20, 2013. We recommend that at least 12 months of long-term registration stability data be submitted with the original NDA. However, the submission of the data of lesser duration will not be considered a reason to Refuse to File that application. The expiration dating period will be assigned based on the quality of the stability data.

**Meeting Discussion:**

The sponsor proposed that 12-month stability data be submitted within 4 months after NDA submission. While agreeing with that proposal, the Agency indicated that the review of the 12-month stability data might be deferred to a later review cycle if the resources available to the Agency at that time were limited. The stability update that the sponsor proposed submitting would not be considered a major amendment to the NDA.

8. Does the Division agree that the complete pharmacology and toxicology program that led to FDA's previous finding of safety and effectiveness for the listed drug Aricept, reference to the completed pharmacology and toxicology program submitted for the approval of Namenda, as well as the additional studies described in this briefing package, support the review and potential approvability of MDX-8704 for the indication of moderate to severe dementia of the Alzheimer's type?

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

9. Does the Division agree with Forest's plan for submitting study-level data sets in the NDA?

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

10. Does the Division agree with the organization of the Electronic Common Technical Document (eCTD) as outlined in the table of contents?

**Preliminary Meeting Comments:**

Yes.

**Meeting Discussion:**

None.

11. In consideration of the indication and intended patient population, does the Agency agree to a full waiver for pediatric studies?

**Preliminary Meeting Comments:**

While your product may in concept qualify for a full waiver for pediatric studies, a final determination in that regard must await further review by the Agency. Please see the section headed "PREA Requirements" below, and especially the text in red font. Significant elements of the same section were conveyed to you immediately prior to the Type C meeting held on June 20, 2013.

**Meeting Discussion:**

The sponsor indicated that a Pediatric Study Plan for MDX-8704 had already been submitted on November 15, 2013, in accordance with the recommendations specified under the heading "PREA Requirements" below (which were also included in the Preliminary Responses), and is to seek a full waiver for pediatric studies of MDX-8704. The sponsor plans to submit a NDA for MDX-8704 in February 2014 and asked if the submission of the Pediatric Study Plan later than 210 days prior to the submission of the NDA could be a reason for the Agency refusing to file the NDA; the Agency indicated that the same scenario would be not be a basis for a Refuse-to-File decision.

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver,

Meeting Minutes

[Insert Meeting Type]

if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). As noted in the draft guidance, for applications submitted on or after January 5, 2014, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **505(b)(2) REGULATORY PATHWAY**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX "TRADENAME"	Previous finding of effectiveness for indication X

3. <i>Example: NDA YYYYYY</i> <i>"TRADENAME"</i>	<i>Previous finding of safety for</i> <i>Carcinogenicity, labeling section XXX</i>
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/  
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ERIC P BASTINGS  
12/17/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 109763

MEETING MINUTES

Adamas Pharmaceuticals Inc.  
Attention: Natalie McClure, Ph.D.  
Sr. Vice President, Product Development  
2200 Powell Street, Suite 220  
Emeryville, CA 94608

Dear Dr. McClure:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ADS-8704.

We also refer to the meeting between representatives of your firm and the FDA on June 20, 2013. The purpose of the meeting was to discuss clinical and CMC issues in preparation for an NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** Guidance  
**Meeting Date and Time:** June 20, 2013 3 PM  
**Meeting Location:** White Oak Bldg. 22, Conference Room 1309  
**Application Number:** 109763  
**Product Name:** MDX-870: Fixed Dose Combination of memantine hydrochloride Extended Release & donepezil hydrochloride Immediate Release  
**Indication:** Alzheimer's Dementia  
**Sponsor/Applicant Name:** Adamas Pharmaceuticals  
**Meeting Chair:** Russell Katz, M.D.

**FDA ATTENDEES**

Russell Katz, M.D. Division Director  
Mani, Ranjit M.D. – Clinical Reviewer  
Nicholas Kozauer, M.D. – Clinical Team Leader  
Martha Heimann, Ph.D. – CMC Team Leader  
Okpo Eradiri, Ph.D. – Biopharmaceutics Reviewer, OMPT/CDER/OPS/ONDQA  
Li Zhang, Ph.D. – Pharmacometrics Reviewer, OMPT/CDER/OTS/OCP/DPM  
Hao Zhu, Ph.D. – Lead Pharmacologist, OMPT/CDER/OTS/OCP/DCPI  
Huixia Zhang, Ph.D. – Senior Staff Fellow, OMPT/CDER/OTS/OCP/DCPI  
Teresa Wheelous, R. Ph. – Sr. Regulatory Management Officer

**ADAMAS Pharmaceuticals & FOREST Research Institute ATTENDEES**

Mary Jean Stempien, M.D., FACP - Vice President, Clinical Research,  
Natalie L. McClure, Ph.D. – Sr. Vice President, Product Development  
June Bray, R.Ph. – Sr. Vice President, Regulatory Affairs, Forest Research Institute, Inc.  
Kerri Z. Kaplan, PharmD. - Manager, Regulatory Affairs, Forest Research Institute, Inc.  
Blake Burrell, M.S - Sr. Manager, Regulatory Affairs-CMC, Forest Research Institute, Inc.  
Andreas Grill, M.B.A - Executive Director, Pharmaceutical R&D, Forest Research Institute, Inc.  
Robert Palmer, M.D. – Sr. Director, Clinical Development, Forest Research Institute, Inc.  
Ramesh Boinpally, Ph.D. - Fellow, Clinical Pharmacology Drug Dynamics, Forest Research Institute, Inc.

## **BACKGROUND**

MDX-870: is a once daily fixed dose combination of the approved products memantine hydrochloride Extended Release & donepezil hydrochloride Immediate Release. An End of Phase 2 meeting was held on October 13, 2011. The objective of this meeting is to obtain guidance and to discuss the remaining clinical and stability requirements for a complete NDA application.

## **DISCUSSION**

### **Question 1:**

**Does the Division agree with the development of fixed dose combinations that include only a 10 mg/day strength for the donepezil component of the drug product?**

### **Preliminary Meeting Response**

Yes.

### **Discussion At Meeting**

None.

### **Question 2a:**

**Given that the Sponsor now intends to use the approved Namenda XR as the memantine component of the FDC, does the Division agree that the safety and efficacy of initiation of memantine using the currently approved three step titration has been adequately established in Forest's NDA 22-525, such that no additional demonstration of safety is required to support the initiation of MDX-8704 in patients with moderate to severe Alzheimer's Disease (AD) on a stable dose of donepezil?**

### **Preliminary Meeting Response**

Yes. However, please also see the following comment.

You initially plan to seek the approval of only 2 fixed combination products of MDX-8704. These are the following:

- A product containing 28 mg of extended-release memantine and 10 mg of donepezil (28/10 formulation)
- A product containing 14 mg of extended-release memantine and 10 mg of donepezil (14/10 formulation)

While we recognize that the 14/10 formulation is intended primarily for patients with severe renal impairment in whom a target dose of Namenda® XR of 14 mg is currently recommended,

should patients without severe renal impairment who happen to be already receiving the 14/10 formulation of MDX-8704 require the administration of a higher dose of extended-release memantine, they will need to first take the 21 mg formulation of Namenda® XR and the 10 mg formulation of donepezil, as separate dosage forms, for at least one week before beginning to take the 28/10 formulation of MDX-8704 to match the current Prescribing Information for Namenda® XR.

**Discussion At Meeting**

None.

**Question 2b:**

[Redacted] (b) (4)

**Preliminary Meeting Response**

[Redacted] (b) (4)

**Discussion At Meeting**

None.

**Question 3:**

**Assuming that bioequivalence is established, does the Division agree that the above indication and dosing and administration language is appropriate, in principle?**

**Preliminary Meeting Response**

We agree with your proposal in concept.

**Discussion At Meeting**

None.

**Question 4:**

**Does the Division agree that 6 months accelerated and long term registration stability is acceptable in the original NDA submission?**

**Preliminary Meeting Response**

We do not agree with your proposal. We recommend that you provide at least 12 months of long- term registration stability data and 6 months of accelerated stability data at the time of

filing of your original NDA submission. Additional stability data received during the review cycle may or may not be reviewed, depending on the resources available to use.

**Discussion At Meeting**

The Agency reiterated its recommendation that at least 12 months of long-term registration stability data be submitted in the original NDA. However, submission of data of lesser duration would not be considered a reason to Refuse to File the application. The expiration dating period will be assigned based on the available data.

**Question 5:**

**Does the Division agree with the proposed stability bracketing design?**

**Preliminary Meeting Response**

Please clarify if all the capsule sizes are the same. If so, your bracketing design is adequate. Otherwise, your stability study should cover the extreme of all design factors including product-to-headspace ratio.

**Discussion At Meeting**

The sponsor acknowledged the Agency's response and will include information to support the bracketing design in the planned NDA.

**Question 6:**

**Does the Division agree that registration stability data from the clinical manufacturing site and release and dissolution comparability data from the commercial site(s) is sufficient in the original NDA submission?**

**Preliminary Meeting Response:**

You need to provide information on the equipment used for (b) (4) and demonstrate that the products are of the same quality and meet the same specification. In this particular instance, stability data from the clinical manufacturing site can be used to support the product shelf life. You should provide release data including dissolution profiles of the three batches made at the commercial site at the time of filing of the NDA. The first three commercial batches should be placed on both accelerated and long term stability. Thereafter, one batch per year should be placed on stability.

Please be aware that per the SUPAC-MR guidance, the site change you have proposed for (b) (4) final steps in the manufacturing process, is a (b) (4) change that requires a bridging bioequivalence study. However, we are willing to consider a proposal to use dissolution testing to bridge the commercial and clinical trial products using a risk-based approach. Please submit your proposal for the comparability protocol that consistently assures the bioequivalence of the commercial product to the clinical batches.

### **Discussion At Meeting**

The sponsor stated that it plans to use dissolution data to bridge the clinical and commercial products and, as recommended, a comparability protocol will be submitted to the Agency.

### **Post-Meeting Note**

If you have an *in vitro in-vivo* correlation developed for your proposed product, the validated model should be used to generate  $C_{max}$  and AUC data in support of the planned bridging.

### **ADDITIONAL BIOPHARMACEUTICS COMMENTS**

1. Please be aware that your lower strength proposed (14/10) product is not proportionally similar to the proposed higher strength (28/10) product. Therefore, you must conduct a bioequivalence study on the 14/10 product as well.

### **Discussion At Meeting**

Although the two strengths are not proportionally similar, the sponsor plans to submit demonstration of an *in vitro-in vivo* correlation for the extended-release component, i.e., memantine hydrochloride, in support of a biowaiver for the lower strength product. In addition, an *in vivo* study demonstrating absence of a pharmacokinetic interaction between donepezil and memantine will be submitted since the *in vivo* study of the proposed *in vitro-in vivo* correlation model was conducted with the memantine component alone. The sponsor also stated that an existing data package will be submitted to the Agency's Biopharmaceutics Classification System (BCS) Committee with the objective of designating donepezil as a BCS (b) (4) drug. Both the BCS classification and the *in vitro-in vivo* correlation data will be used to support the biowaiver request in the NDA.

2. We recommend that you follow the Agency Biopharmaceutics advice provided at the Type B meeting held on October 13, 2011.

### **Discussion At Meeting**

The sponsor remains cognizant of the advice provided by the Agency at the Type B meeting held on October 13, 2011

### **PREA REQUIREMENTS**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).

- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

#### **Discussion At Meeting**

The sponsor is to submit a request for a waiver for pediatric studies.

### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **Discussion At Meeting**

The sponsor is aware of the aforementioned data standards.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information

required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

**Discussion At Meeting**

The sponsor asked whether an abuse potential assessment would be in fact be required for MDX-8704, given that its component drugs do not exhibit any abuse potential.

The Agency confirmed that no abuse potential assessment would be required for MDX-8704.

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/s/  
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ERIC P BASTINGS

07/12/2013



IND 109763

MEETING MINUTES

Adamas Pharmaceuticals, Inc.  
Attention: Natalie McClure, Ph.D.  
Vice President, Regulatory Affairs  
1900 Powell Street, Suite 1050  
Emeryville, CA 94608

Dear Dr. McClure:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ADS-8704 extended release capsules.

We also refer to your June 29, 2011, correspondence requesting an End of Phase 2 meeting to discuss your proposed Phase 3 development plan.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on October 13, 2011. The purpose of the meeting was to discuss your proposed Phase 3 development plan.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** October 13, 2011  
**Meeting Location:** White Oak Bdg. 22, Conference Room 1309  
**Application Number:** 109763  
**Product Name:** Memantine & Donepezil  
**Indication:** Alzheimer's Disease  
**Sponsor Name:** Adamas Pharmaceuticals Inc.  
**Meeting Chair:** Russell Katz, M.D.

**FDA ATTENDEES**

Russell Katz, MD - Division Director  
Ranjit Mani, MD - Clinical Reviewer  
Nicholas Kozauer, MD - Clinical Reviewer  
Lois Freed, PhD - Nonclinical Supervisor  
David Hawver, PhD - Nonclinical Reviewer  
Angela Men, PhD - Clinical Pharmacology Team Leader  
Martha Heimann, PhD - CMC Lead  
Xinning Yang, PhD - Clinical Pharmacology Reviewer  
Jingyu Luan, PhD - Biometrics Reviewer  
Teresa Wheelous, R. Ph - Sr. Regulatory Project Manager

**ADAMAS PHARMACEUTICALS ATTENDEES**

Mary Jean Stempien, MD - Clinical Development, Consultant  
Gayatri Sathyan, PhD - Vice President, Clinical Pharmacology  
Gregory Went, PhD - Chief Executive Officer  
Charles S. Davis, Ph.D. - Biostatistician, Consultant  
Pierre N. Tariot, MD - Dementia Specialist, Consultant  
Natalie L. McClure, PHD - Vice President, Clinical and Regulatory Affairs

## **BACKGROUND**

The June 29, 2011 End of Phase 2 meeting request was granted July 8, 2011, and the meeting package was received September 9, 2011.

The purpose of this meeting is to discuss the ongoing development of ADS-8704 for the treatment of Alzheimer's disease (AD). Specifically, the sponsor is proposing a Phase 3 study (Protocol ADS-DEM-DM302) that seeks to investigate the safety and tolerability of ADS-8704 in patients with moderate to severe AD (who are on stable doses of donepezil at Screening).

## **DISCUSSION QUESTIONS:**

- 1) Since the approval of Namenda in the US in 2003, it is estimated that 1.6 million patient years of memantine/donepezil exposure in combination have been recorded in the US (IMS Health) alone. The efficacy of memantine alone has been established (NDA 21-487, (Reisberg, Doody et al. 2003)). The efficacy of donepezil has been also established (NDA 20-690, (Rogers, Doody et al. 1998)). The efficacy of memantine as add-on therapy to donepezil/cholinesterase inhibitors has been established (NDA 21-487, (Tariot, Farlow et al. 2004), 2004 and NDA 22-525, (Grossberg, Manes et al. 2008)).
  - a. Does the Division agree that the efficacy of the co-administration of memantine and donepezil has been sufficiently evaluated in MEM-MD-50 (Grossberg, Manes et al. 2008) and MEM-MD-02 (Tariot, Farlow et al. 2004), that no additional demonstration of the efficacy of the combination of memantine and donepezil is required to support an NDA submission for ADS-8704?

### **Preliminary Meeting Comments:**

Yes, we agree.

### **Discussion at Meeting:**

None

- b. Adamas proposes that it is not necessary to establish the contribution of components to the observed clinical effect in support of an ADS-8704 NDA. Does the Division agree?

### **Preliminary Meeting Comments:**

Yes, we agree.

### **Discussion at Meeting:**

None

- c. Does the Division agree that a single phase 3 safety and tolerability study of ADS-8704 administered without titration (ADS-DEM-DM302), is sufficient to support an NDA?

**Preliminary Meeting Comments:**

While we agree that a single Phase 3 safety and tolerability study of ADS-8704 could support the submission of an NDA in form, we do not agree with the currently proposed design of Study ADS-DEM-AD302 as reflected in our response to Question 2 below.

**Discussion at Meeting:**

None

- d. Does the Division agree that a safety database on 200 subjects receiving ADS-8704 from ADS-DEM-DM302 is sufficient?

**Preliminary Meeting Comments:**

Yes, we agree.

**Discussion at Meeting:**

None

- 2) In support of an NDA for ADS-8704, Adamas proposes to conduct a single phase 3 study, ADS-DEM-DM302 (synopsis provided in Appendix 11.1), which will be a randomized controlled clinical study evaluating the safety and tolerability of ADS-8704 administered to 400 subjects randomized between ADS-8704 and placebo comparator for 6 weeks without initial dose titration. As described in the briefing document, in support of this proposed study, Adamas has conducted the ADS-DEM-ME110 study, and demonstrated in healthy volunteers that an ER formulation of memantine was well tolerated when administered without dose titration.
- a. Adamas believes that the memantine ER component of ADS-8704 has adequate similarity to Namenda XR with respect to composition and pharmacokinetics and the donepezil component is bioequivalent to Aricept such that study ADS-DEM-DM302 can be safely initiated. Does the Division agree?

**Preliminary Meeting Comments:**

No, we do not agree. As reflected in the meeting minutes for the March 2, 2009 End-of-Phase 2 meeting held under IND (b) (4), we continue to have significant concerns about the safety of memantine ER (in this case 28 mg) when dosed without titration in patients with moderate to severe Alzheimer's disease (as is proposed for Study ADS-DEM-AD302).

As you note, the Clinical Pharmacology studies that were conducted with ADS-8704 without a memantine titration (NPI-5002-C-106 and ADS-DEM-ME110) enrolled young healthy volunteer subjects. Findings from these trials, therefore, cannot be reliably extrapolated to patients with moderate to severe AD who can be expected to frequently have multiple medical comorbidities. Similarly, the literature review provided in your submission only references studies in Alzheimer's disease patients that have dosed memantine at a maximum initial daily starting dose of 10 mg. Furthermore, the combined use of donepezil and memantine in clinical practice provides little additional

reassurance as it must be assumed that these agents were started individually, as well as titrated, in almost all cases.

Therefore, if you intend to conduct Study ADS-DEM-DM302 as currently designed, we require that the dose of ADS-8704 (which includes 28 mg memantine HCl ER) be reached by titration using the currently approved product labeling for Namenda<sup>TM</sup> as a guide.

Alternatively, we would consider adequate safety findings from a smaller inpatient safety study of several weeks duration in patients with moderate to severe Alzheimer's disease, in which a dose of 28 mg of memantine ER could be administered without titration, as potentially supportive of a larger outpatient Phase 3 trial such as Study ADS-DEM-DM302.

**Discussion at Meeting:**

The sponsor indicated that although they still believe that the evidence submitted to the Division in the briefing package for this meeting in favor of dosing ADS-8704 without a memantine titration supports the safety of this approach, they have accepted the Division's requirement that ADS-8704 be dosed only with a memantine titration in Study ADS-DEM-302 as proposed in the submission.

The sponsor expressed some reservations related to the ability to successfully conduct a smaller inpatient study in patients with moderate-to-severe Alzheimer's disease where ADS-8704 would be dosed without a memantine titration (as suggested as a potential path forward in the Division's preliminary meeting comments). Specifically, the sponsor suggested that the theoretically difficult adjustment of Alzheimer's disease patients with relatively advanced disease to an inpatient setting might complicate the interpretation of safety data, for example. In response to a question from the sponsor, the Division indicated that an inpatient duration of 2 weeks during such a trial would likely be sufficient in order to demonstrate the safety of dosing ADS-8704 without a memantine titration. The Division also expressed agreement with the sponsor's proposal that a smaller 2-week inpatient safety study (with memantine titration) could be incorporated into a larger safety study such as ADS-DEM-302 (where ADS-8704 would be dosed without titration), assuming acceptable safety findings from the initial phase. The Division further indicated that a sample size of approximately 30 subjects who were randomized in a 2:1 ratio of active treatment to placebo would likely be acceptable for the initial inpatient phase of such a study. Additionally, the Division agreed that adequate safety data obtained from an inpatient trial that enrolled Alzheimer's disease patients in the earlier stages of the disease (who could theoretically tolerate an inpatient stay more easily) could also potentially support the conduct of a larger outpatient safety study in patients with moderate-to-severe disease.

If, however, a shorter inpatient safety study was ultimately found not to be feasible, the sponsor indicated that they would titrate memantine in a traditional 3-step titration (i.e. 5 mg once daily for a week, 5 mg twice daily for a week, 5 mg each morning and 10 mg each evening for a week, and then 20 mg twice daily for a week) prior to the initiation of Study ADS-DEM-302. The Division indicated that this approach would be acceptable

from a safety standpoint and is in line with the recommendation in the preliminary meeting comments. The Division further clarified, however, that there is likely little to be learned from Study ADS-DEM-302 if conducted with this titration as the combined use of donepezil and memantine is generally accepted as safe based both on evidence from clinical trials as well as the widespread concomitant use of these drugs in clinical practice.

Finally, the sponsor suggested that they are also considering an outpatient safety study design where subjects would first be dosed with 14 mg memantine ER for 1 week prior to dosing with ADS-8704 (i.e. a “1-step titration”). The sponsor argued that there are published studies utilizing more aggressive titrations of memantine as compared to the recommended 3-step approach, as submitted in the recent briefing package [particularly Jones and Bayer *et al.* (2007)], which would support the safety of this 1-step titration approach (also keeping in mind that the assertion that the  $C_{max}$  of the 14 mg memantine ER formulation is approximately equivalent to the 10 mg memantine IR formulation). Additionally, the sponsor pointed out that a study conducted by the manufacturer of Namenda® (Forest Pharmaceuticals Inc.) has also dosed memantine IR in a 1-step titration of 10 mg for 1 week then increasing to 20 mg. The Division agreed that a 1-step titration beginning with 14 mg memantine ER for 1 week prior to dosing with ADS-8704 may be acceptable in form assuming that the sponsor could demonstrate that the relevant studies in the literature included adequate safety monitoring of subjects. Additionally, the Division suggested that the sponsor also attempt to obtain additional information from Forest as to the conduct of their relevant trial which has apparently not been published.

- b. Does the Division agree with the proposed study design?

**Preliminary Meeting Comments:**

Please see our preceding response to question 2a.

**Discussion at Meeting:**

Please refer to the meeting discussion under question 2a.

- c. Does the Division agree that a 6 week treatment period is sufficient to characterize the safety and tolerability of ADS-8704 administered without titration?

**Preliminary Meeting Comments:**

In principle, we do not object to the 6 week duration of the proposed trial for the purpose of characterizing the safety and tolerability of ADS-8704, but please refer to our response to question 2a regarding our concerns about the lack of a memantine titration in the study.

**Discussion at Meeting:**

Please refer to the meeting discussion under question 2a.

- 3) For the NDA submission, Adamas proposes to conduct two pharmacokinetic studies: A single dose PK study (ADS-DEM-DM102) comparing ADS-8704 to Namenda XR co-

administered with Aricept to establish bioequivalence; and a second study to evaluate the food effect (ADS-DEM-DM103).

- a. Both studies will use the 28 mg memantine ER and 10 mg donepezil IR formulation. The lower dose strengths will not be evaluated. Does the Division agree?

**Preliminary Meeting Comments:**

It is acceptable. Please see the below Biopharmaceutics comments about the requirements for biowaiver.

**Discussion at Meeting:**

None

- b. The food effect study (ADS-DEM-DM103) will include a third arm where ADS-8704 will be administered by opening the capsule and sprinkling the contents on applesauce. Does the Division agree?

**Preliminary Meeting Comments:**

Yes.

**Discussion at Meeting:**

None

- c. Because the multiple dose pharmacokinetics of memantine ER have been evaluated in study ADS-DEM-ME110, and shown to be similar on a dose adjusted basis to Namenda XR, Adamas is not proposing to conduct any additional multiple dose PK studies. Does the Division agree?

**Preliminary Meeting Comments:**

It is acceptable, pending the results of your proposed single-dose BE study, ADS-DEM-DM102.

**Discussion at Meeting:**

None

## **ADDITIONAL PRELIMINARY MEETING COMMENTS**

**Nonclinical:**

We would like to address the issue raised in your submission of July 22, 2010 to IND (b) (4) regarding the need for an acute-dose neurotoxicity study in rats with memantine, given alone and in combination with donepezil. We continue to recommend that the study be conducted concurrent with Phase 3 clinical trials; however, if the study is not available at the time of NDA submission, it will not be a filing or approvability issue. If the NDA is approved without the study, it will be a post-marketing requirement, unless we have determined that you no longer need to conduct the study.

### **Biopharmaceutics:**

#### **Bioavailability or Bioequivalence (BA/BE) Waiver Request:**

You may request a waiver for the CFR's requirement to provide BA/BE data for the lower strengths of your proposed memantine ER/donepezil IR product. The biowaiver request should be supported by the following information: **1)** acceptable BA/BE data for the highest strength, **2)** formulation information demonstrating that the proposed lower strengths are compositional proportional to the highest strength, and **3)** comparative multimedia dissolution profile data and  $f_2$  values (i.e., pHs 1.2, 4.6, and 6.8) generated for the memantine ER and donepezil IR components, using the same testing conditions.

#### **Dissolution Method:**

Provide the reports for the proposed dissolution methods evaluating the extended release (ER) memantine component and the immediate release (IR) donepezil component of your proposed product. The reports should include the complete dissolution profile data collected during the development and validation of the proposed dissolution method(s). A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method(s) as most appropriate should be included in the report. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The dissolution profile should be complete and cover at least  $(b)(4)$  % of drug dissolved or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable. The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified. Also, include the testing conducted to demonstrate the discriminating capability of the selected test(s) as well as the validation data for the method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method(s) should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.

#### **Dissolution Acceptance Criteria**

**ER Component:** Provide the dissolution profile data from the clinical and stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the drug dissolution acceptance criteria, the following points should be considered:

- The in vitro dissolution profile should encompass the timeframe over which at least  $(b)(4)$  % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
- For extended release products the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set. The acceptance criteria ranges should be based on the overall dissolution data generated at these times.
- In general, the selection of the dissolution specification ranges is based on mean target value  $(b)(4)$  % and NLT  $(b)(4)$  % for the last specification time-point. Wider specification

ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.

- Data from lots used in the clinical trials and primary stability studies should be used and the dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

**IR Component:** The setting of the acceptance criterion should be based on the overall dissolution profile data from the bio-batches and primary stability batches. The following points should be considered:

- The dissolution profile should encompass the timeframe over which at least  $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
- The specification-time point should be set when  $Q = \frac{(b)}{(4)}$ % of dissolution occurs.

**In Vitro Alcohol Induced Dose Dumping:**

We acknowledge that you are planning to evaluate the in vitro alcohol induced dose dumping for your product. Please note that first you should conduct the in vitro alcohol induced dose dumping testing; however, depending on the result of this testing you may have to follow-up with an in vivo alcohol-dose dumping study. Note that if the results show an interaction of your product with alcohol, you should discuss these results with FDA prior to NDA submission.

The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your product:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the in vitro dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
- In general;
  - If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.
  - If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.
  - If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
  - If the dissolution of the MR product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.
- The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).

- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

**Extended Release Claim:**

Based on the Code of Federal Regulations, [21 CFR 320.25 (f)\*], if any part of your drug product includes an extended-release component, you should provide the steady-state fluctuation index (FI) data supporting the approval of the controlled-release claims made for your drug product (i.e., *the drug's fluctuation index (peak to valley ratio; Cmax/Cmin) from the steady-state study comparing the test-product to that of the reference-product must be measured. The ER claim will be supported if the FI value for the test-product is lower than the FI value from the reference.*

**Pre-Meeting Comments from the Sponsor:**

The following comments were sent to the Division via electronic-mail by the sponsor on October 12, 2011 in response to the Division's preliminary meeting comments:

Our team has met to discuss the preliminary review comments. We thank you for the clear feedback. We will not need any additional discussions on questions 1 and 3. We will want to use the meeting time to discuss the overall development path. We understand the Division's requirement for use of the currently approved titration labeling as a guide in the safety study DM302. We would like to obtain some additional clarity on the Division's thinking with regard to dose titration. In addition, we would like to discuss other considerations around the conduct of an inpatient safety study in Alzheimer's patients.

In anticipation of this program moving forward, we would like to explore what the label indication and dosing language might look like for the two patient groups who would be expected to benefit from ADS-8704: 1) those patients who are receiving donepezil and ready to start therapy with ADS 8704 and 2) those patients who are currently receiving both donepezil and memantine and would be candidates for switching to ADS 8704. We had not discussed the latter group in our briefing package, but since titration is not an issue with this group, we anticipate that the requirements for this label might be minimal.

We have two questions for the biopharmaceutics reviewer. It may be possible to respond to these in writing rather than in person.

- 1) Please confirm that the multimedia dissolution studies described on page 4 (point three under biowaiver) are needed at the highest strength rather than at all strengths.
- 2) We are confused by the language regarding the Extended Release label claim, since we will not be conducting an additional steady state study (as noted in question 3c). Could you please explain the impact of not having the label claim. We are expecting a similar label to that granted to Namenda XR.

**Additional Discussion at Meeting:**

The Division indicated that if the 28mg memantine ER component of ADS-8704 was found to be bioequivalent to the approved formulation of 28 mg Namenda XR<sup>®</sup>, this finding would likely be sufficient to support the limited marketing approval of ADS-8704 for the treatment of patients

with moderate-to-severe Alzheimer's disease who are already taking stable doses of 20 mg memantine and 10 mg donepezil (assuming that the bioequivalence results for the 10 mg donepezil component of ADS-8704 in relation to Aricept<sup>®</sup> were also deemed acceptable). In other words, no additional safety study with ADS-8704 would be required in this scenario.

**Additional Biopharmaceutics Responses:**

The Division is also including in these meeting minutes the following responses to the sponsor's additional biopharmaceutics questions which were not discussed during the October 13, 2011 meeting:

- 1) Please confirm that the multimedia dissolution studies described on page 4 (point three under biowaiver) are needed at the highest strength rather than at all strengths.

**Division Response:**

The multipoint dissolution profile comparison at the different pH media should be conducted for all the strengths. For the estimation of the similarity  $f_2$  values, the higher strength (used for the in vivo BA/BE study) should be used as the reference product.

- 2) We are confused by the language regarding the Extended Release label claim, since we will not be conducting an additional steady state study (as noted in question 3c). Could you please explain the impact of not having the label claim. We are expecting a similar label to that granted to Namenda XR.

**Division Response:**

If your product is shown to be bioequivalent to the reference extended release (ER) product, your product will have the ER claim. However, in the event that your product is not bioequivalent to the reference ER product, you should explain how are you planning to fulfill the CFR 320.25 (f) requirements for ER formulations.

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/s/  
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RUSSELL G KATZ  
10/31/2011