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APPLICATION NUMBER:

206439Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW ADDENDUM – NDA 206439

Office of New Drug Quality Assessment

Application No.:	206-439	**Biopharmaceutics Reviewer:** Okpo Eradiri, Ph.D.	
Division:	DNP		
Applicant:	Forest Laboratories, Inc.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D	
Trade Name:	Namzaric Capsules	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Memantine HCl ER/Donepezil Capsules	**Date Assigned:**	3/5/2014
Indication:	Treatment of moderate to severe dementia of the Alzheimer's type.	**Date of Addendum:**	11/21/2014.
Formulation/strength	FDC Tablet, Memantine HCl ER/ Donepezil HCl: 14/10 mg & 28/10 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission dates	CDER Stamp Date	Primary Review due in DARRTS	PDUFA DATE
2/26/2014, 6/10/2014, 8/7/2014, 11/21/2014	2/26/2014	10/26/2014	12/26/2014

Type of Submission:	NDA; 505(b)(2)
Type of Consult:	505 (b)(2) Application (Relied upon product: NDA 20-690 (Aricept approved Nov 25, 1996)) Associated IND: 109-763
Key Review Points:	Final Biopharmaceutics recommendation on approvability of NDA 206439

SYNOPSIS:

This document is an addendum to the original Biopharmaceutics review by Dr. Okpo Eradiri, uploaded into Panorama on October 26, 2014.

Background: At the time of completion of the original review of NDA 206439, the Biopharmaceutics recommendation was PENDING because the following two items were outstanding:

1. Finalization of the dissolution acceptance criteria for both active components. In an IR dated 10/31/2014, the Applicant was asked to update the Specification Table with the FDA-recommended dissolution acceptance criteria; and
2. The Office of Scientific Investigations had not submitted their report for the inspection of the analytical site of BE study MDX-PK-104.

Review: The purpose of this Addendum to the original NDA review is to update the two items and finalize the Biopharmaceutics recommendation on the approvability of this NDA.

1. **Finalization of the dissolution acceptance criteria for both active components:**
The Applicant responded to the IR on 11/21/2014 (SDN 9, Sequence # 008 in DARRTS) accepting FDA's recommended dissolution acceptance criteria. The Specification Tables for both strengths of the FDC Capsules (Memantine HCl/Donepezil HCl ER FDC Capsules, 14/10 mg and 28/10 mg) have been updated with the recommended dissolution acceptance criteria:

<table>
<tr><th>USP Apparatus</th><th>Spindle Rotation</th><th>Medium/ Volume/Temperature</th><th>Acceptance Criteria</th></tr>
<tr><td rowspan="6">1 (basket)</td><td rowspan="6">100 rpm</td><td rowspan="6">900 ml of NaCl/HCl buffer, pH 1.2 at 37 ± 0.5 °C</td><td>Donepezil:
Q = (b) (4)% at 15 min</td></tr>
<tr><td>Memantine:</td></tr>
<tr><td>
<table>
<tr><th>Time (hours)</th><th>Limits</th></tr>
<tr><td>1</td><td>NMT (b) (4)%</td></tr>
<tr><td>4</td><td>(b) (4)%</td></tr>
<tr><td>8</td><td>%</td></tr>
<tr><td>12</td><td>NLT (b) (4)%</td></tr>
</table>
</td></tr>
</table>

2. **OSI Inspection Report on the bioanalytical Site for Study MDX-PK-104:**
The OSI report on the definitive BE study (#MDX-PK-104), uploaded into DARRTS on 11/14/2014 by Dr. Gajendiran Mahadevan, concluded that "the data were found to be reliable".

RECOMMENDATION

ONDQA/Biopharmaceutics had reviewed NDA 206439 and its amendments submitted on 2/26/2014, 6/10/2014, 8/7/2014, 11/21/2014, and found the biopharmaceutics data/information acceptable.

The following dissolution method and acceptance criteria should be implemented for release and stability testing of Memantine HCl ER/Donepezil Capsules:

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	**Donepezil**: Q = (b) (4) % at 15 min **Memantine**:

Time (hours)	Limits
1	NMT (b) (4) %
4	(b) (4) %
8	%
12	NLT (b) (4) %

From the Biopharmaceutics perspective, NDA 206439 for Memantine HCl ER/Donepezil Capsules is recommended for **APPROVAL**.

Okponanabofa Eradiri, Ph.D.
Digitally signed by Okponanabofa Eradiri, Ph.D.
DN: cn=Okponanabofa Eradiri, Ph.D., o=ONDQA, ou=Biopharmaceutics, email=okpo.eradiri@fda.hhs.gov, c=US
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Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13000708 43, cn=Angelica Dorantes -S
Date: 2014.11.21 20:04:55 -05'00'

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

APPENDIX

INFORMATION REQUEST SENT TO APPLICANT ON 10/31/2014

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) (approved in 2010) to (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:

<table>
<tr><th>USP Apparatus</th><th>Spindle Rotation</th><th>Medium/ Volume/Temperature</th><th>Acceptance Criteria</th></tr>
<tr><td rowspan="6">1 (basket)</td><td rowspan="6">100 rpm</td><td rowspan="6">900 ml of NaCl/HCl buffer, pH 1.2 at 37 ± 0.5 °C</td><td>Donepezil:
Q = (b) (4)% at 15 min</td></tr>
<tr><td>Memantine:</td></tr>
<tr><td>Time (hours) | Acceptance Limits</td></tr>
<tr><td>1 | NMT (b) (4)%</td></tr>
<tr><td>4 | (b) (4) %</td></tr>
<tr><td>8 | %</td></tr>
<tr><td>12 | NLT (b) (4)%</td></tr>
</table>

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

APPLICANT'S RESPONSE SUBMITTED ON 11/21/2014 (SDN 9 IN DARRTS)

The sponsor agrees to the FDA-recommended dissolution acceptance criteria for memantine HCl extended release / donepezil HCl capsules. This submission provides the revised release and stability drug product specifications for both dosage strengths (section 3.2.P.5.1 (14 mg/10 mg) and section 3.2.P.5.1 (28 mg/10 mg)). The drug product stability protocol will be amended accordingly. Section 3.2.P.8.2 is provided for reference.

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