

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206439Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## BIOPHARMACEUTICS REVIEW ADDENDUM – NDA 206439

### Office of New Drug Quality Assessment

<b>Application No.:</b>	206-439	<b>Biopharmaceutics Reviewer:</b>	
<b>Division:</b>	DNP	Okpo Eradiri, Ph.D.	
<b>Applicant:</b>	Forest Laboratories, Inc.	<b>Biopharmaceutics Team Leader:</b>	
<b>Trade Name:</b>	Namzarcic Capsules	Angelica Dorantes, Ph.D.	
<b>Generic Name:</b>	Memantine HCl ER/ Donepezil Capsules	<b>Date Assigned:</b>	3/5/2014
<b>Indication:</b>	Treatment of moderate to severe dementia of the Alzheimer's type.	<b>Date of Addendum:</b>	11/21/2014.
<b>Formulation/strength</b>	FDC Tablet, Memantine HCl ER/ Donepezil HCl: 14/10 mg & 28/10 mg		
<b>Route of Administration</b>	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
<b>Type of Submission:</b>	NDA; 505(b)(2)		
<b>Type of Consult:</b>	505 (b)(2) Application (Relied upon product: NDA 20-690 (Aricept approved Nov 25, 1996)) Associated IND: 109-763		
<b>Key Review Points:</b>	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:

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

**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	<b>Donepezil:</b> Q = (b)(4)% at 15 min							
			<b>Memantine:</b> <table border="1"> <thead> <tr> <th>Time (hours)</th> <th>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>%</td> </tr> <tr> <td>12</td> <td>NLT (b)(4)%</td> </tr> </tbody> </table>	Time (hours)	Limits	1	NMT (b)(4)%	4	(b)(4)%	8
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**.

**Okponanabof  
a 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  
 Date: 2014.11.21 19:59:58 -05'00'

**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=1300070843, 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:

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>	
			<b>Time (hours)</b>	<b>Acceptance Limits</b>
			1	NMT (b) (4)%
			4	(b) (4)%
8	%			
12	NLT (b) (4)%			

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.

## Clinical Pharmacology Review

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PRODUCT (Generic Name):	Memantine HCl Extended Release and Donepezil HCl Immediate-Release Fixed Dose Combination
PRODUCT (Brand Name):	Namzaric
NDA:	206,439
DOSAGE FORM:	Capsule
DOSAGE STRENGTHS:	28 mg/10 mg, 14 mg/10 mg (memantine/donepezil)
INDICATION:	Moderate or severe dementia of Alzheimer's Type
SUBMISSION DATE:	02/26/2014
APPLICANT:	Forest Research Institute, Inc.
CP REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

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Namzaric™ (MDX-8704) is a fixed-dose combination (FDC) of memantine extended-release (ER) and donepezil immediate-release (IR). Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. It was approved for treatment of Alzheimer's Disease (AD) under NDAs 21-487 (IR tablet), 21-627 (oral solution), and 22-525 (ER capsule). Donepezil is an acetylcholinesterase inhibitor (AChEI). It was approved for treatment of AD under NDAs 20-690 (IR tablet), 21-719 (oral solution), 21-720 (oral disintegrating tablet), and 22-568 (higher strength of tablet).

MDX-8704 is a capsule formulation consisting of memantine HCl ER (b)(4) and donepezil HCl IR (b)(4). MDX-8704 is available as two strengths: 28 mg memantine HCl ER/ 10 mg donepezil HCl and 14 mg memantine HCl/10 mg donepezil HCl. The proposed indication for MDX-8704 is the treatment of moderate to severe dementia of the Alzheimer's type (AD). The higher strength is for use in patients currently stabilized on memantine HCl (10 mg twice daily IR tablet or 28 mg once daily ER capsule) and donepezil HCl 10 mg. The lower strength is only for use in patients with severe renal impairment currently stabilized on memantine HCl (5 mg twice daily IR tablet or 14 mg once daily ER capsule) and donepezil 10 mg. MDX-8704

administered as a once-daily FDC regimen may simplify administration, increase compliance and adherence to treatment, and thus provide benefit for patients and their caregivers.

The applicant submitted this NDA as a 505(b)(2) application which relies on previous findings of safety and effectiveness for the reference list drugs, Aricept (NDA 20-690) as well as Namenda and Namenda XR (NDAs 21-487 and 22-525). In the past, a clinical trial was conducted to compare efficacy/safety of Namenda XR to placebo in patients with moderate to severe AD already on AChEIs. That study showed Namenda XR added onto donepezil provided statistically significant improvement relative to donepezil alone for one of the co-primary efficacy endpoints, the SIB (severe impairment battery), and numerical improvement (not statistically significant) on the other primary endpoint, the CIBIC-plus (clinician interview-based impression of change with caregiver input rating score). Treatment of moderate to severe AD with concurrent memantine and donepezil is the current standard of care.

The applicant did not conduct efficacy trials and pursued approval based on demonstration of bioequivalence (BE) between the 28/10 mg MDX-8704 (28 mg memantine ER and 10 mg donepezil IR) capsule and co-administration of the 28 mg Namenda XR<sup>®</sup> capsule (memantine ER) and 10 mg Aricept<sup>®</sup> tablet (Study MDX-PK-104). The applicant also conducted a PK study (MDX-PK-105) to evaluate the food effect on MDX-8704 and compare administration of the intact 28/10 mg MDX-8704 capsule and capsule contents sprinkled on applesauce. In addition, biowaivers for the drug product manufactured at commercial manufacturing site, and for the lower MDX-8704 strength (14/10 mg) were requested. This was based on comparison of predicted PK parameters (AUC and  $C_{max}$ ) derived from *in vitro* dissolution data and an established *in vitro-in vivo* correlation (IVIVC) model for memantine ER. Please refer to the review documented by Biopharmaceutical reviewer, Dr. Okpo Eradiri, for review on the BE study and biowaiver request.

This review focuses on Study MDX-PK-105. The major findings are:

- There was no significant food effect on bioavailability of (AUC and  $C_{max}$ ) of memantine and donepezil administered as MDX-8704.
- Administration of MDX-8704 as capsule contents sprinkled on applesauce is bioequivalent to administration of intact capsule (both under fasted conditions), for memantine and donepezil.
- The median  $T_{max}$  was reduced to 14 hours from 24 hours for memantine when administered with food. Such  $T_{max}$  change is similar to the food effect described in the labeling of Namenda XR<sup>®</sup> (updated on September 26, 2014):  
*There is no difference in memantine exposure, based on  $C_{max}$  or AUC, for NAMENDA XR whether that drug product is administered with food or on an empty stomach. However, peak plasma concentrations are achieved about 18 hours after administration with food versus approximately 25 hours after administration on an empty stomach.*  
*There is no difference in the absorption of NAMENDA XR when the capsule is taken intact or when the contents are sprinkled on applesauce.*

- The median  $T_{max}$  of donepezil was prolonged to 6 hours when MDX-8704 was administered with high-fat meal, compared to 3 hours under fasted condition. The median  $T_{max}$  of donepezil was reduced from 3 to 2 hours when MDX-8704 was administered as capsule contents sprinkled on applesauce compared to administration of intact capsule. Such changes are not considered clinically relevant, since MDX-8704 is used to treat a chronic disease.

Overall, no clinically significant PK difference was observed for memantine or donepezil when MDX-8704 was administered with food or sprinkled on applesauce.

In conclusion, the information submitted under NDA 206-439 has been reviewed and found to be acceptable from the Clinical Pharmacology's perspective.

**Study MDX-PK-105: A Single-Center, Randomized, Open-Label, 3-Way Crossover, Single-Dose Study in Healthy Adults to Evaluate the Effect of Food and the Effect of Administration of Capsule Contents Sprinkled on Applesauce on the Relative Bioavailability of Memantine and Donepezil After Oral Administration of MDX-8704 (Study Period: Apr 19, 2013 – July 12, 2013)**

Objective	<p>1. To evaluate the effect of food on the relative bioavailability of memantine and donepezil after oral administration of an intact MDX-8704 capsule.</p> <p>2. To evaluate the relative bioavailability of memantine and donepezil after oral administration of MDX-8704 as an intact capsule and capsule contents sprinkled on applesauce in the fasted state.</p>																									
Study Design	<p>Subjects were randomly assigned to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA). Each of the following treatments was administered with a 21-day washout period between treatments:</p> <p>Treatment A: A single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg capsule administered under fasted conditions</p> <p>Treatment B: A single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg capsule administered following a high-fat breakfast</p> <p>Treatment C: A single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg administered as capsule contents sprinkled on 30 mL (2 tablespoons) of applesauce under fasted conditions</p>																									
Study Population	<p>Thirty-six subjects were enrolled in the study (25 males and 11 females). Three subjects prematurely discontinued, one due to an adverse event (AE), one due to a protocol violation, and one subject for other reasons. The mean age (<math>\pm</math> SD) and body mass index (<math>\pm</math> SD) were 27.3 (<math>\pm</math> 5.3) years and 25.41 (<math>\pm</math> 2.90) kg/m<sup>2</sup>, respectively. Twenty-five subjects were white and 10 subjects were black.</p>																									
Pharmacokinetic Assessments	<p>Blood samples were collected starting on Day 1 of each period at 0 hour (predose) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 264 hours after dosing.</p> <p>The PK parameters, C<sub>max</sub>, T<sub>max</sub>, AUC<sub>t</sub>, AUC<sub>inf</sub>, and T<sub>1/2</sub>, were estimated using non-compartmental approach.</p> <p>Descriptive statistics for all PK parameters of memantine and donepezil were provided for all subjects who completed the study, had no episode of emesis (within 24 hours after administration of MDX-8704 for PK analysis of memantine and within 2 times the median T<sub>max</sub> after administration of MDX-8704 for PK analysis of donepezil), and had evaluable PK parameters. The C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-inf</sub> of memantine and donepezil were compared by means of a linear mixed effects model with sequence, treatment, and period as fixed effects and subjects within sequence as a random effect. The Wilcoxon signed-rank test was performed on T<sub>max</sub>. A p-value <math>\leq</math> 0.05 was considered a significant difference between treatments.</p>																									
Bioanalytical Method	<p>The bioanalytical assays were validated and are acceptable.</p> <table border="1"> <thead> <tr> <th>Analyte</th> <th>Memantine (ng/ml)</th> <th>Donepezil (ng/ml)</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>LC-MS/MS</td> <td>LC-MS/MS</td> </tr> <tr> <td>Internal Standard</td> <td><sup>2</sup>H-memantine</td> <td><sup>2</sup>H-donepezil</td> </tr> <tr> <td>LLOQ</td> <td>0.50</td> <td>0.50</td> </tr> <tr> <td>Calibration Range</td> <td>0.5, 1, 2, 5, 10, 20, 40, 50</td> <td>0.5, 1, 2, 5, 10, 20, 40, 50</td> </tr> <tr> <td>QC</td> <td>1.5, 8, 30</td> <td>1.5, 8, 30</td> </tr> <tr> <td>Accuracy(% Bias)</td> <td><math>\pm</math> 2%</td> <td><math>\pm</math> 5.3%</td> </tr> <tr> <td>Precision (%CV)</td> <td>3.0%</td> <td>4.2%</td> </tr> </tbody> </table>		Analyte	Memantine (ng/ml)	Donepezil (ng/ml)	Method	LC-MS/MS	LC-MS/MS	Internal Standard	<sup>2</sup> H-memantine	<sup>2</sup> H-donepezil	LLOQ	0.50	0.50	Calibration Range	0.5, 1, 2, 5, 10, 20, 40, 50	0.5, 1, 2, 5, 10, 20, 40, 50	QC	1.5, 8, 30	1.5, 8, 30	Accuracy(% Bias)	$\pm$ 2%	$\pm$ 5.3%	Precision (%CV)	3.0%	4.2%
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Accuracy(% Bias)	$\pm$ 2%	$\pm$ 5.3%																								
Precision (%CV)	3.0%	4.2%																								

Safety	Adverse events (AEs), vital sign, clinical laboratory evaluations, electrocardiographic (ECG), physical examination, and Columbia-Suicide Severity Rating Scale (C-SSRS)
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### Results

Because of emesis, 10 subjects were excluded from the PK analysis of the Treatments A and B comparison, and 12 subjects were excluded from the PK analysis of the Treatments A and C comparison. The PK parameters and profiles of memantine and donepezil are shown as below.

Table 1. Pharmacokinetic Parameters (Mean ± SD) for Memantine—Pharmacokinetic Population

Parameter	Treatment A Mean ± SD (n = 23)	Treatment B Mean ± SD (n = 23)	Ratio of Geometric LS Means (B/A)	90% CI of the Ratio or p-Value
C <sub>max</sub> , ng/mL	27.901 ± 5.618	29.973 ± 6.368	1.067	0.989 - 1.152
AUC <sub>0-t</sub> , ng•h/mL	2865.103 ± 616.849	2913.386 ± 670.739	1.011	0.937 - 1.090
AUC <sub>0-∞</sub> , ng•h/mL	3056.252 ± 736.229 <sup>a</sup>	3096.443 ± 762.100	1.014	0.936 - 1.099
T <sub>max</sub> , h <sup>b</sup>	24.000 (12.00, 36.00)	14.000 (12.00, 30.02)	0.76	0.014 <sup>c</sup>
T <sub>1/2</sub> , h	62.067 ± 13.365 <sup>d</sup>	59.745 ± 11.548	—	—
Parameter	Treatment A Mean ± SD (n = 23)	Treatment C Mean ± SD (n = 21)	Ratio of Geometric LS Means <sup>e</sup> (C/A)	90% CI of the Ratio or p-Value <sup>e</sup>
C <sub>max</sub> , ng/mL	27.901 ± 5.618	30.081 ± 5.362	1.080	1.009 - 1.156
AUC <sub>0-t</sub> , ng•h/mL	2865.103 ± 616.849	3112.814 ± 633.168	1.069	0.990 - 1.154
AUC <sub>0-∞</sub> , ng•h/mL	3056.252 ± 736.229 <sup>a</sup>	3337.457 ± 798.017	1.090	1.003 - 1.185
T <sub>max</sub> , h <sup>b</sup>	24.000 (12.00, 36.00)	14.000 (12.00, 36.00)	0.77	0.012 <sup>c</sup>
T <sub>1/2</sub> , h	62.067 ± 13.365 <sup>d</sup>	62.768 ± 15.540	—	—

a. For AUC<sub>0-inf</sub>, n = 22 for comparison between Treatments A and B and n = 20 between Treatments A and C because reliable AUC<sub>0-inf</sub> value could not be calculated for Subject 001-0016.

b. For T<sub>max</sub>, the median (minimum - maximum) and arithmetic mean ratios are presented for the treatment comparison.

c. The Wilcoxon signed-rank test was performed to calculate the p-value for the comparison of T<sub>max</sub>.

d. For T<sub>1/2</sub>, n = 22 for Treatment A because reliable value could not be calculated for Subject 001-0016.

e. n = 21 for statistical comparisons of Treatment A versus Treatment C because Subjects 001-0010 and 001-0033 were excluded due to vomiting after receiving Treatment C.

Figure 1. Mean (± SD) Plasma Concentrations of Memantine Versus Time by Treatment — PK Population

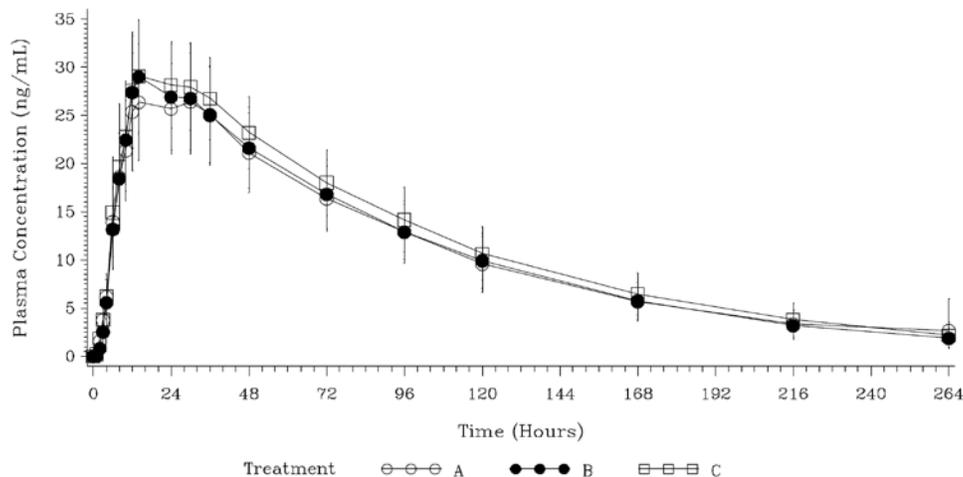


Table 2. Pharmacokinetic Parameters (Mean ± SD) for Donepezil—Pharmacokinetic Population

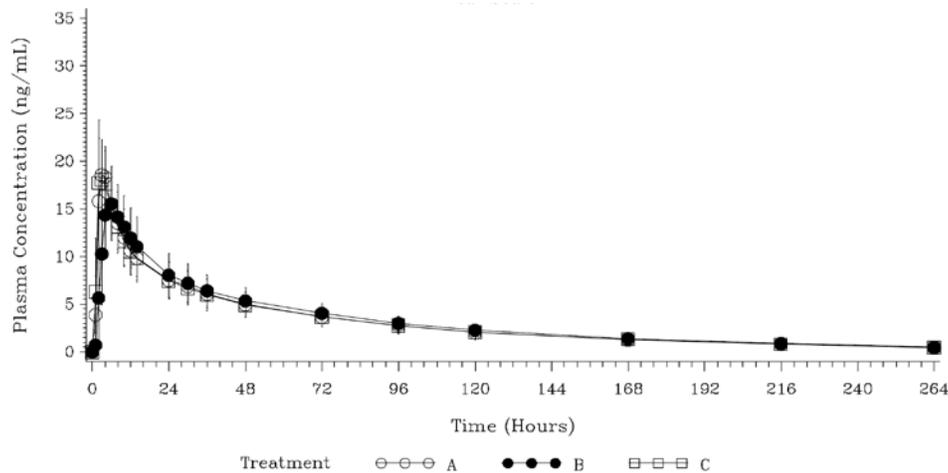
Parameter	Treatment A Mean ± SD (n = 23)	Treatment B Mean ± SD (n = 23)	Ratio of Geometric LS Means (B/A)	90% CI of the Ratio or p-Value
C <sub>max</sub> , ng/mL	20.113 ± 3.892	17.299 ± 2.953	0.862	0.825 - 0.901
AUC <sub>0-t</sub> , ng•h/mL	802.752 ± 190.313	847.712 ± 204.953	1.054	1.013 - 1.096
AUC <sub>0-∞</sub> , ng•h/mL	875.346 ± 208.617	915.888 ± 219.479	1.044	1.003 - 1.087
T <sub>max</sub> , h <sup>a</sup>	3.000 (2.00, 4.05)	6.000 (2.00, 10.00)	1.74	<0.001 <sup>b</sup>
T <sub>1/2</sub> , h	67.258 ± 12.405	66.615 ± 9.716	—	—
Parameter	Treatment A Mean ± SD (n = 23)	Treatment C Mean ± SD (n = 21)	Ratio of Geometric LS Means <sup>c</sup> (C/A)	90% CI of the Ratio or p-Value <sup>c</sup>
C <sub>max</sub> , ng/mL	20.113 ± 3.892	20.315 ± 4.407	0.987	0.926 - 1.053
AUC <sub>0-t</sub> , ng•h/mL	802.752 ± 190.313	803.039 ± 220.399	0.983	0.942 - 1.025
AUC <sub>0-∞</sub> , ng•h/mL	875.346 ± 208.617	874.062 ± 243.792	0.981	0.938 - 1.026
T <sub>max</sub> , h <sup>a</sup>	3.000 (2.00, 4.05)	2.067 (2.00, 4.00)	0.91	0.278 <sup>b</sup>
T <sub>1/2</sub> , h	67.258 ± 12.405	65.007 ± 13.140	—	—

a. For T<sub>max</sub>, the median (minimum - maximum) and arithmetic mean ratios are presented for the treatment comparison.

b. The Wilcoxon signed-rank test was performed to calculate the p-value for the comparison of T<sub>max</sub>.

c. n = 21 for statistical comparisons of Treatment A versus Treatment C because Subjects 001-0010 and 001-0033 were excluded due to vomiting after receiving Treatment C.

Figure 2. Mean (± SD) Plasma Concentrations of Donepezil Versus Time by Treatment — PK Population



Food has no significant effect on the bioavailability of the MDX-8704 capsule. The median T<sub>max</sub> was reduced to 14 hours from 24 hours for memantine, but was prolonged to 6 hours from 3 hours for donepezil when administered with the high-fat meal compared to under fasted conditions.

Administration of MDX-8704 as capsule contents sprinkled on applesauce is bioequivalent to administration of intact capsule. The median T<sub>max</sub> of memantine was reduced to 14 hours from 24 hours and the T<sub>max</sub> of donepezil was reduced to 2.1 hours from 3.0 hours when administered as capsule contents sprinkled on applesauce compared to administration of intact capsule.

Safety	Overall, 28 subjects (77.8%) reported treatment-emergent adverse events (TEAEs) considered to be related to investigational product. The most common TEAEs (> 10%
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	<p>of all subjects) were nausea (69.4%), dizziness (50.0%), vomiting (33.3%), headache (27.8%), and abdominal discomfort (13.9%). The incidence of TEAEs was similar following administration of MDX-8704 under fasted conditions either as an intact capsule (62.9% of subjects) or as capsule contents sprinkled on applesauce (67.7% of subjects); the incidence of TEAEs was lower (44.1% of subjects) following administration of MDX-8704 intact capsule under fed conditions.</p> <p>The incidence of nausea and vomiting was similar following administration of MDX-8704 under fasted conditions either as an intact capsule (57.1% and 28.6% of subjects, respectively) or as capsule contents sprinkled on applesauce (55.9% and 23.5% of subjects, respectively) and was lower following administration of MDX-8704 intact capsule under fed conditions (35.3% and 5.88% of subjects, respectively).</p> <p>The majority of the TEAEs were mild to moderate in severity. All the incidences of vomiting were moderate in severity. The incidence of moderate nausea was similar for the 2 treatments administered under fasted conditions (intact capsule, 25.7%; capsule contents sprinkled on applesauce, 23.5%) and lower following MDX-8704 administered as an intact capsule under fed conditions (5.88%).</p> <p>No clinically meaningful trends were observed in clinical laboratory, vital sign, or 12-lead electrocardiogram results. No subject reported suicidal ideation or suicidal behavior.</p>
Conclusions	<p>No clinically significant PK difference in memantine or donepezil was observed when MDX-8704 was administered with food or sprinkled on applesauce.</p>

**LABELING RECOMMENDATIONS**

The reviewer looked through the applicant’s proposed labeling for Namzaric™ and found it acceptable from Clinical Pharmacology’s perspective, provided that the recommended revisions are made to the labeling language.

Labeling recommendation to be sent to the applicant:

The text in red color is the reviewer’s proposed addition to the labeling; the strikethrough text is recommended by the reviewer for deletion.

*(Reviewer’s Note: It seems that the applicant’s proposed labeling was modified based on merged labelings of Aricept® and Namenda XR®. Only newly added language and the one subject to recommended changes are shown below. The language same as that in Aricept® or Namenda XR® labelings is not included here.)*

**HIGHLIGHT**

Drug Interactions

[Redacted text block] (b) (4)

[Large redacted text block] (b) (4)

## 7 DRUG INTERACTIONS

(b) (4)

### 8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. TRADENAME (b) (4) **has not been studied** in patients with severe hepatic impairment [see (b) (4) Clinical Pharmacology (12.3)].

### 12.3 Pharmacokinetics

TRADENAME

(b) (4)

Exposure (AUC and  $C_{max}$ ) of memantine and donepezil following TRADENAME administration in the fed or fasted state was similar. Further, exposure of memantine and donepezil following TRADENAME administration as intact capsule or capsule contents sprinkled on applesauce was similar in healthy subjects.

#### Hepatic Impairment

(b) (4)

#### Drug-Drug Interactions

##### Use with Cholinesterase Inhibitors

Coadministration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. **Furthermore, memantine did not affect AChE inhibition by donepezil.** In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

##### Effect of Memantine on the Metabolism of Other Drugs

Pharmacokinetic studies evaluated the potential of memantine for interaction with (b) (4) **warfarin** and bupropion (b) (4)

(b) (4) Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion.

Furthermore, memantine did not affect the pharmacokinetics or pharmacodynamics of warfarin as assessed by the prothrombin INR.

#### Effect of Other Drugs on Memantine

Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A (b) (4) single-dose of bupropion did not affect the pharmacokinetics of memantine at steady state.

*(Reviewer's Note: The sentence describing the effect of bupropion on memantine does not exist in the current labeling of either Namenda or Namenda XR. However, in the Clinical Pharmacology review for Namenda XR which was documented by Dr. Huixia Zhang in DARRTS and also shown on Drugs@FDA, it was concluded that no effect of memantine on bupropion or on CYP2B6 activity (hydroxylation of bupropion) was found, nor was there an effect of bupropion on memantine. So, it seems acceptable to add the description of bupropion's effect on memantine PK in the current labeling for Namzaric™.)*

#### Donepezil HCl

(b) (4)  
Donepezil is (b) (4) absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours.

Xinning Yang, Ph.D.  
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D. Ph.D. \_\_\_\_\_

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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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XINNING YANG  
11/14/2014

YUXIN MEN  
11/16/2014

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	206-439	<b>Biopharmaceutics Reviewer:</b> Okpo Eradiri, Ph.D.	
<b>Division:</b>	DNP		
<b>Applicant:</b>	Forest Laboratories, Inc.	<b>Biopharmaceutics Team Leader:</b> Angelica Dorantes, Ph.D	
<b>Trade Name:</b>	Namzaric	<b>Acting Biopharmaceutics Supervisor:</b> Paul Seo, Ph.D.	
<b>Generic Name:</b>	Memantine HCl ER/Donepezil Capsules	<b>Date Assigned:</b>	3/5/2014
<b>Indication:</b>	Treatment of moderate to severe dementia of the Alzheimer's type.	<b>Date of Review:</b>	10/26/2014.
<b>Formulation/strength</b>	FDC Tablet, Memantine HCl ER/ Donepezil HCl: 14/10 mg & 28/10 mg		
<b>Route of Administration</b>	Oral		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Submission dates</b>	<b>CDER Stamp Date</b>	<b>Primary Review due in DARRTS</b>	<b>PDUFA DATE</b>
2/26/2014, 6/10/2014, 8/7/2014	2/26/2014	10/26/2014	12/26/2014
<b>Type of Submission:</b>	NDA; 505(b)(2)		
<b>Type of Consult:</b>	505 (b)(2) Application (Relied upon product: NDA 20-690 (Aricept approved Nov 25, 1996)) Associated IND: 109-763		
<b>Key Review Points:</b>	<ul style="list-style-type: none"> <li>- Adequacy of the dissolution method and acceptance criteria for both components</li> <li>- Assessment of alcohol dose dumping experimental results</li> <li>- Adequacy of the design, conduct and results of definitive bioequivalence study on the highest strength, 28/10 mg (Memantine HCl/Donepezil)</li> <li>- Validity of the IVIVC Model for the ER Component of the FDC Product</li> <li>- Acceptability of the biowaiver request for the lower strength, 14/10 mg</li> <li>- Acceptability of the biowaiver request for the manufacturing site change</li> </ul>		
<b>SUMMARY OF BIOPHARMACEUTICS FINDINGS:</b>			
<p><b>Submission:</b> NDA 206439 is a 505(b)(2) submission for Memantine HCl ER (b)(4) combined with immediate-release Donepezil HCl (b)(4) in a capsule. The proposed drug product is a FDC extended-release dosage form because one of the active components is an ER formulation. The two active drugs were previously approved: Memantine HCl (NDA's 21487 &amp; 22525) and Donepezil (NDA 20690). Both drugs have been shown to improve cognitive function in patients with moderate to severe Alzheimer's disease.</p>			

**Review:** The Biopharmaceutics review is focused on the following:

1. Adequacy of the dissolution method and acceptance criteria for both components
2. Assessment of alcohol dose dumping experimental results
3. Adequacy of the design, conduct and results of the definitive bioequivalence study on the highest strength, 28/10 mg (Memantine HCl/Donepezil)
4. Validity of the IVIVC model for the ER memantine component of the proposed FDC Memantine HCl/Donepezil product
5. Acceptability of the two biowaiver requests

It is noted that this NDA also included a food-effect/applesauce study and other drug-drug interaction (DDI) studies. The Office of Clinical pharmacology is reviewing these studies.

**1. Dissolution Information**

a) **Dissolution Method:** The Applicant proposes the same dissolution method that was approved for single-entity Memantine HCl ER Capsules in the quality control of Memantine HCl ER/ Donepezil HCl FDC Capsules. Although the method results in (b) (4) release of donepezil from the immediate-release (b) (4) it is acceptable because the Applicant's data package demonstrate that donepezil drug substance is highly soluble and highly permeable.

b) **Dissolution Acceptance Criteria:**

The following dissolution method and acceptance criteria for Memantine HCl/Donepezil HCl ER FDC Capsules, 14/10 mg and 28/10 mg, are recommended:

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							
			<table border="1"> <thead> <tr> <th>Time (hours)</th> <th>Limits</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>(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>(b) (4)</td> </tr> </tbody> </table>	Time (hours)	Limits	1	(b) (4)	4	(b) (4)	8
Time (hours)	Limits									
1	(b) (4)									
4	(b) (4)									
8	(b) (4)									
12	(b) (4)									

**2. Alcohol Dose Dumping**

The Applicant observed alcohol dose dumping of the memantine component in 40% alcohol and has submitted a justification for not conducting an in-vivo study. A definitive BE study (MDX-PK-104) comparing the proposed FDC tablet to the co-administered single entity products serves as the basis for approval of this NDA; this study has been reviewed by the Biopharmaceutics team. Food-effect/applesauce and DDI studies (to be reviewed by OCP) were also conducted.

**3. Bioequivalence Study for the Higher Strength**

A definitive BE study (MDX-PK-104) comparing the proposed FDC tablet to the co-administered single entity products serves as the basis for approval of this NDA. The

memantine and donepezil components in the higher strength of the FDC capsules have been demonstrated to be bioequivalent to their respective single-entity reference products and BE study MDX-PK-104 is acceptable, provided the Office of Scientific Investigations does not identify any critical issues for this BE study.

**4. Validity of the IVIVC Model for the ER-Memantine component of the FDC product**

In order to apply the established IVIVC model (in NDA 22525) to the memantine component of the FDC capsules in this NDA (206439) to support the biowaiver requests, the predicted memantine PK parameters for the higher strength of the FDC (28/10 mg) were compared to those for the target (clinical batch) in NDA 22525. The IVIVC's predicted FDC-memantine: Observed Namenda XR ratios for  $C_{max}$ ,  $AUC_t$ , and  $AUC_{\infty}$  are 104.59, 113.85, and 112.89 %, respectively. The corresponding ratios for the Observed FDC: Observed Namenda XR are 96.94, 106.79, and 107.21, respectively. Since all ratios are within 20% of the target single-entity product, application of the IVIVC model to this NDA is adequately supported and therefore this model is considered valid for the memantine component of the FDC product.

**5. Biowaiver Requests**

- a) **Manufacturing Site Change:** The Applicant's supporting data for the manufacturing site change biowaiver request are adequate. The request for a waiver of bioavailability study on the proposed drug product manufactured at the clinical and commercial sites is therefore granted.
- b) **Lower Strength:** The Applicant's comparative dissolution data for the low (14/28 mg) and high (28/10 mg) strengths of the FDC product have been demonstrated to be similar. The request for a waiver of bioavailability study on the lower strength is therefore granted.

**6. Risk Assessment**

Initial Risk Assessment			Final Risk Assessment			
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk approach	Mitigation	Risk Evaluation	Lifecycle Considerations/ Comments**
Dissolution Donepezil	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	Low		(b) (4) The dissolution profile of the donepezil (b) (4) should meet specification due to its high solubility and the (b) (4)	Acceptable	No comments since donepezil is rapidly dissolving, is highly soluble and highly permeable.
Dissolution Memantine	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials (rate controlling polymers)</li> <li>• API sources</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	Medium	The drug (b) (4)	(b) (4)	Acceptable	-Adhere to SUPAC-MR guidelines for minor and major changes. -For changes in the container closure system, adequate stability/dissolution data should be

			in HDPE bottles. (b) (4)		evaluated due to potential effect on release rate.
<b>Alcohol Dose Dumping</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	High	Even though the product has a pronounced dose dumping with 40% alcohol, clinical trials indicate mild adverse events for doses up to 100mg.	Acceptable	Changes in formulation require evaluating potential alcohol dose dumping.

Please see the CMC review for the other CQAs.

**RECOMMENDATION**

At this time of the review process (GRMP date), the dissolution acceptance criteria for the proposed drug product have not been finalized. In addition, the Office of Scientific Investigations has not submitted their report for the inspection of the analytical site of BE study MDX-PK-104. Therefore, from the Biopharmaceutics perspective critical information needed to support the approval of this NDA is incomplete and the Biopharmaceutics recommendation on the approvability of NDA 206439 is currently **PENDING**.

**Okpo Eradiri, Ph. D.**  
 Biopharmaceutics Reviewer  
 Office of New Drug Quality Assessment

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

## TABLE OF CONTENTS

SUMMARY OF BIOPHARMACEUTICS FINDINGS: .....	1
RECOMMENDATION .....	4
TABLE OF CONTENTS.....	5
<b>1</b> INTRODUCTION.....	6
<b>2</b> PROPOSED DISSOLUTION METHOD .....	7
2.1. Reviewer’s Assessment: SATISFACTORY .....	10
<b>3</b> SETTING OF DISSOLUTION ACCEPTANCE CRITERIA .....	10
<b>3.1</b> Applicant’s Proposed Acceptance Criterion - Donepezil .....	10
<b>3.2</b> Applicant’s Proposed Acceptance Criteria - Memantine.....	11
Reviewer’s Assessment: NOT SATISFACTORY .....	11
<b>4.</b> ALCOHOL DOSE DUMPING.....	13
4.1. Reviewer’s Assessment: SATISFACTORY .....	14
<b>5.</b> BIOEQUIVALENCE STUDY MDX-PK-104.....	14
5.1. Study Number: MDX-PK-104 .....	14
5.2. Study Title .....	14
5.3. Objectives.....	15
5.4. Design.....	15
5.5. Analytes, Parameters and Statistics.....	15
5.6. Results .....	17
5.7. Reviewer’s Assessment of BE Study: PENDING .....	18
<b>6.</b> VALIDITY OF THE IVIVC MODEL.....	19
<b>7.</b> BIOWAIVER REQUESTS .....	19
7.1. Biowaiver for Site change (from NY to Ireland) .....	20
Reviewer’s Assessment: SATISFACTORY.....	22
7.2. Biowaiver for 14/10 mg strength of the FDC capsule .....	22
Reviewer’s Assessment: SATISFACTORY.....	24
<b>8.</b> RISK EVALUATION .....	25
Reviewer’s Assessment: SATISFACTORY.....	25

# 1 INTRODUCTION

**Background:** The associated IND for this Application is 109763. The Applicant is combining two previously approved drugs: Memantine HCl (NDAs 21487 & 22525) and Donepezil (NDA 20690). Both drugs have been shown to improve cognitive function in patients with moderate to severe Alzheimer’s disease.

**Review:** The Biopharmaceutics review will be focused on the evaluation and acceptability of the following:

- Adequacy of the dissolution method and acceptance criteria for both components
- Assessment of alcohol dose dumping experimental results
- Adequacy of the design, conduct and results of the definitive bioequivalence study on the highest strength, 28/10 mg (Memantine HCl/Donepezil)
- Acceptability of the biowaiver requests for the lower strength, 14/10 mg and for the manufacturing site change

**Drug Product:**

The Memantine HCl ER/Donepezil HCl FDC Capsules comprise combination of the Memantine HCl ER (b) (4) (approved in NDA 22525) and Donepezil HCl (b) (4); the later were made by (b) (4). The compositions of the two proposed strengths of the FDC capsules are presented in Tables 1 (14/10 mg) and 2 (28/10 mg).

**Table 1: Composition of proposed Memantine HCl ER/Donepezil HCl FDC Capsules, 14/10 mg (from Module 3, section 3.2.P.1)**

Component	Function	Quality Standard	Unit Dose Composition		
			(% w/w)	mg/capsule	
<b>Memantine HCl ER Beads</b>					
Memantine HCl	Drug substance (b) (4)	In-house	7.4	14	
Povidone (b) (4) USP		USP/NF		(b) (4)	
Talc, USP		USP/NF			
Sugar spheres (b) (4) NF (b) (4)		USP/NF			
		In-house <sup>c</sup>			
		USP/NF			
		In-house <sup>d</sup>			
Donepezil HCl, USP	Drug substance (b) (4)	USP/NF	5.3	10	
Lactose monohydrate, NF		USP/NF		(b) (4)	
Microcrystalline cellulose, NF		USP/NF			
Corn starch, NF		USP/NF			
Colloidal silicon dioxide, NF		USP/NF			
Magnesium stearate, NF		USP/NF			
Total filled weight		---			
Empty gelatin capsule, size 2		In-house <sup>c</sup>			
Total Theoretical Memantine HCl ER/Donepezil HCl Capsules, 14 mg/10 mg				249.9	

**Table 2: Composition of proposed Memantine HCl ER/Donepezil HCl FDC Capsules, 28/10 mg (from Module 3, section 3.2.P.1)**

Component	Function	Quality Standard	Unit Dose Composition	
			(% w/w)	mg/capsule
<b>Memantine HCl ER Beads</b>				
Memantine HCl	Drug substance	In-house	10.1	28
Povidone (b) (4) USP	(b) (4)	USP/NF		(b) (4)
Talc. USP		USP/NF		
Sugar spheres (b) (4) NF	(b) (4)	USP/NF		
		In-house <sup>c</sup>		
		USP/NF		
		In-house <sup>d</sup>		
Donepezil HCl, USP		USP/NF	3.6	10
Lactose monohydrate, NF		USP/NF		(b) (4)
Microcrystalline cellulose, NF		USP/NF		
Corn starch, NF		USP/NF		
Colloidal silicon dioxide, NF		USP/NF		
Magnesium stearate, NF		USP/NF		
<b>Total filled weight</b>		----		
Empty gelatin capsule, size 1		In-house <sup>e</sup>		
<b>Total Theoretical Memantine HCl ER/Donepezil HCl Capsules, 28 mg/10 mg</b>				<b>353.9</b>

It is obvious from the quantitative compositions of the two strengths that the formulations of the proposed higher and lower strengths are not proportional.

## 2 PROPOSED DISSOLUTION METHOD

The proposed dissolution method was approved for Memantine HCl extended-release capsules in NDA 22525; since the same extended-release (b) (4) are contained in the proposed FDC Capsules, suitability of the method will be assessed for donepezil only through the dissolution method validation.

Dissolution Apparatus: USP Apparatus (basket)  
 Dissolution Medium: NaCl/HCl buffer, pH 1.2  
 Temperature: 37 ± (b) (4) °C  
 Dissolution Volume: 900 mL  
 Rotation Speed: 100 rpm  
 Sampling Times: Memantine - 1, 4, 8, and 12 h  
 Donepezil - (b) (4) min  
 Sampling Volume: 1 mL

Memantine concentration in dissolution samples is measured using HPLC-UV with (b) (4) (Table 3). The same chromatographic system is used to quantify

#### 4. ALCOHOL DOSE DUMPING

The Applicant investigated the influence of 5, 10, 20, and 40 % alcohol on the dissolution rate of the proposed FDC capsules. On the basis of the results obtained on both strengths of the FDC product, the Applicant concluded that pronounced dose dumping occurred with 40% alcohol (Figure 5).

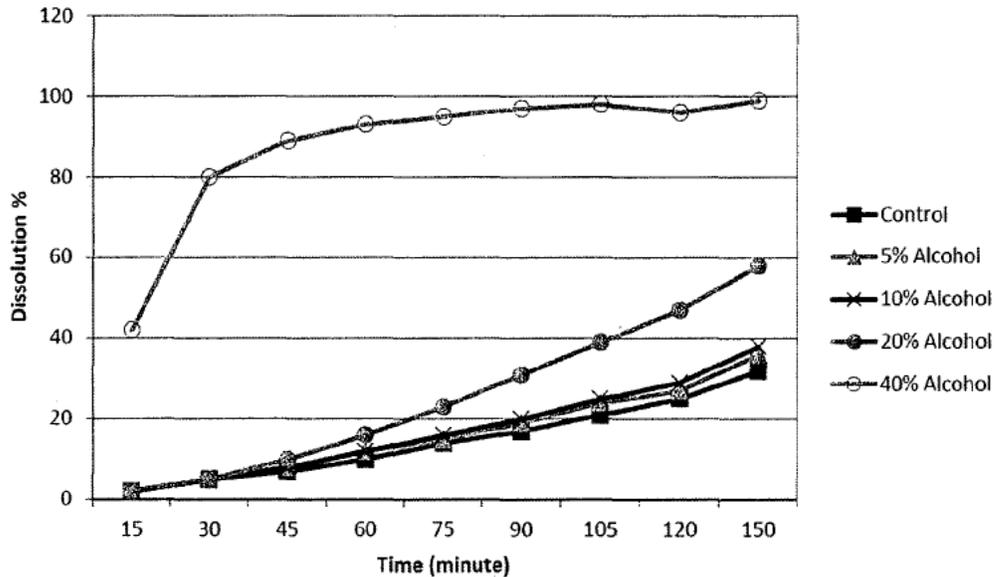


Figure 5: Effect of alcohol on dissolution of Memantine HCl/Donepezil HCl ER Capsules, 28/10 mg [USP Apparatus 1, 900 mL pH 1.2 NaCl/HCl buffer, 100 rpm; n = 12]; similar results were observed for the 14/10 mg strength.

#### **4.1. Reviewer's Assessment: SATISFACTORY**

Although the Applicant did not explain the potential clinical implications of the dose dumping observed for the memantine component, it is obvious that the results of the alcohol dose dumping studies are similar to the approved single-entity product in NDA 22-525. Dr. Lillian Zhang, the Clinical Pharmacology Reviewer for the single-entity under NDA 22525, commented on the in-vitro alcohol dose dumping as follows:

The extreme situation of dose dumping with 40% alcohol means that the entire capsule dose of 28 mg would be released in 30-45 minutes, i.e., ER is behaving as an IR. Based on simulation, 28 mg XR QD and 28 mg IR QD have comparable concentration at steady state. Single 40 mg doses of memantine were safe and well tolerated. In order to understand the impact of a patient receiving a bolus of memantine 28 mg, the sponsor has looked at the adverse events for memantine in worldwide post marketing and clinical trials experience for doses up to 100 mg. The majority of the events included dizziness, somnolence, confusion, vertigo, weakness and vomiting. There were no deaths in overdoses up to 100 mg. Further, data from clinical trials for other indications where the daily dose was over 20 mg, reaching up to 100 mg, revealed the same events as mentioned above, and were mild in intensity and reversible. Overall, the events were mild and reversible. Efficacy will not be decreased with one incidence or infrequent consumption of alcohol. Thus, there is no concern about alcohol consumption from a clinical pharmacology standpoint.

*\*For specific details refer to Dr. Zhang's Clin Pharm review in DARRTS dated 5/3/2010.*

Since the proposed FDC capsules contain the same memantine HCl ER (b)(4), the Applicant will not be asked to conduct an in-vivo alcohol dose dumping study.

### **5. BIOEQUIVALENCE STUDY MDX-PK-104**

One bioavailability study was conducted by the Applicant in healthy subjects under fasting conditions to investigate the bioequivalence of each of the active components to their respective Listed Drug Products (LDP) as follows:

Memantine 28 mg	-	Namenda™ XR Capsules 28 mg (Forest, NY)
Donepezil 10 mg	-	Aricept Tablets, 10 mg (Eisai, Inc.)

This pivotal bioequivalence study is the clinical basis for approval of the proposed fixed-dose combination product.

#### **5.1. Study Number: MDX-PK-104**

#### **5.2. Study Title**

A Single-Center, Randomized, Open-Label, 2-Way Crossover, Single-Dose Study Evaluating the Bioequivalence of Memantine HCl Extended Release and Donepezil HCl Fixed-Dose Combination (MDX-8704) Versus Co-administered Namenda XR™ and Aricept® in Healthy Subjects.

### 5.3. Objectives

- Investigation of bioequivalence of test FDC product to co-administration of respective single-entity RLD's of the active components, memantine HCl and donepezil HCl.
- Evaluation of safety profile of the test product relative to reference treatment.

*Reviewer's Note: Please refer to the Clinical Review for assessment of the safety data.*

### 5.4. Design

- Open-label, single-dose, fasting, randomized, 2-treatment, 2-period, 2-sequence, crossover in 38 healthy, adult subjects (25M, 13F) aged 19 - 45 years (mean age 29.8 y) with BMI between 18.9 and 30.0 kg/m<sup>2</sup>. Study participants also met all other inclusion and exclusion criteria.
- 38 subjects enrolled; PK-evaluable subjects were 23 for memantine and 24 for donepezil.
- Drug products administered after at least 10 h fast:

*Test:* One Memantine HCl/Donepezil HCl extended release Capsule, 28-mg/10 mg (Forest Research Institute; Batch # BN00023559)

*References:* One Namenda XR™ Capsule, 28 mg (Forest Labs, Ireland), and one Aricept® Tablet, 10 mg (Eisai, Inc.)

- Washout period: 21 days
- Blood sampling (6 mL): pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 264 h after drug administration.
- Anticoagulant: K<sub>2</sub>EDTA

### 5.5. Analytes, Parameters and Statistics

Memantine and Donepezil in plasma were quantified by an HPLC-Mass spectrometry method. The linear calibration range for both analytes was 0.5 – 50 ng/mL. The assay performance during sample analysis, as determined by QC's, standard curves, incurred sample reanalysis as well as the validation parameters are acceptable. The summary of the in-study assay performance is provided in Table 7.

The long-term stability established for memantine and donepezil in plasma is 131 days at -30 °C and 126 days at -70 °C. The first study dose was given to study participants on Apr 26, 2013 and the last bioanalytical run occurred on Jul 5, 2013, a total of 71 days. Plasma samples from this study were flash frozen and stored at -70 °C until analysis. The long term stability duration therefore adequately covers the period of storage of the samples.

**Table 7: Summary of bioanalytical method for memantine and donepezil:  
Validation and in-study performance**

Matrix	Human Plasma (K <sub>2</sub> EDTA)	
Sample Volume Required	100 µL	
Storage Conditions	-30°C (Plasma study samples, Standards & QCs)	
Extraction Procedure	Off-line Automated Liquid-Liquid Extraction using methyl <i>tert</i> -butyl ether, after basification of plasma samples.	
Concentration Range	0.5 to 50 ng/mL for memantine & donepezil	
Analytical Methodology	Method #354: Bioanalytical Method for the Determination of Memantine and Donepezil in Human Plasma by LC-MS/MS	
Detection	LC-MS/MS, ESI positive mode	
Regression Type	Linear with 1/x <sup>2</sup> weighing	
Coefficient of Determination (r <sup>2</sup> )	Memantine: ≥0.9984 Donepezil: ≥0.9943	
Between-Batch Accuracy (%deviation)	Standards (n = 4)	-3.0 to 2.0 (memantine); -6.0 to 4.0 (donepezil)
	QCs (n = 24)	-2.7 to 1.6 (memantine); -4.7 to -2.1 (donepezil)
Between-Batch Precision (%CV)	Standards (n = 4)	0.3 to 3.1 (memantine); 1.6 to 10.6 (donepezil)
	QCs (n = 24)	2.0 to 2.9 (memantine); 2.0 to 5.6 (donepezil)
Within-Batch CV (%)	Accuracy (%)	within ±4.0 (memantine); within ±7.3 (donepezil)
	CV (%)	≤3.4 (memantine); ≤2.2 (donepezil)
Recovery	Drug Reference	58% - 62% (memantine); 44% - 51% (donepezil)

Stability in human plasma	Room temp	Established for 24 hours
	Freeze/thaw	4 freeze-thaw cycles with freezing at -30°C established
	Long term	131 days @ -30°C; 126 days @ -70°C
Solution Stability	at room temp	NA
	at 4°C	Internal Standard Spiking Solution (ISSS): 64 days established
Reference Solution Stability	at room temp	Memantine Stock: 24 hrs. Donepezil Stock: 27 hrs. [ <sup>2</sup> H <sub>6</sub> ] memantine & [ <sup>2</sup> H <sub>7</sub> ] donepezil: 23 hrs. established
	at 4°C	NA
LLOQ (Accuracy (%deviation) / Precision (%CV))	Memantine: -4.0 / 6.3 Donepezil: -6.0 / 10.6	
Processed Stability	at 5°C	54.5 hrs. established
Dilution Integrity (v:v sample-blank)	1:3 for QC.3 1:9 for AULOQ QC	

Coefficient of Determination (r <sup>2</sup> )	Memantine: ≥0.9968 Donepezil: ≥0.9959	
Between-Batch Accuracy (%deviation)	Standards (n = 32)	-1.8 to 2.0 (memantine); -3.6 to 1.4 (donepezil)
	QCs (including outliers), n = 64	-1.9 to -0.6 (memantine); -6.7 to -2.9 (donepezil)
	QCs (excluding outliers)	-1.1 to 0.0 (memantine); -5.3 to -2.4 (donepezil)
Between-Batch Precision (%CV)	Standards (n = 32)	1.3 to 4.0 (memantine); 2.0 to 5.0 (donepezil)
	QCs (including outliers), n = 64	4.8 to 6.0 (memantine); 5.7 to 6.4 (donepezil)
	QCs (excluding outliers)	2.0 to 4.0 (memantine); 2.8 to 4.9 (donepezil)

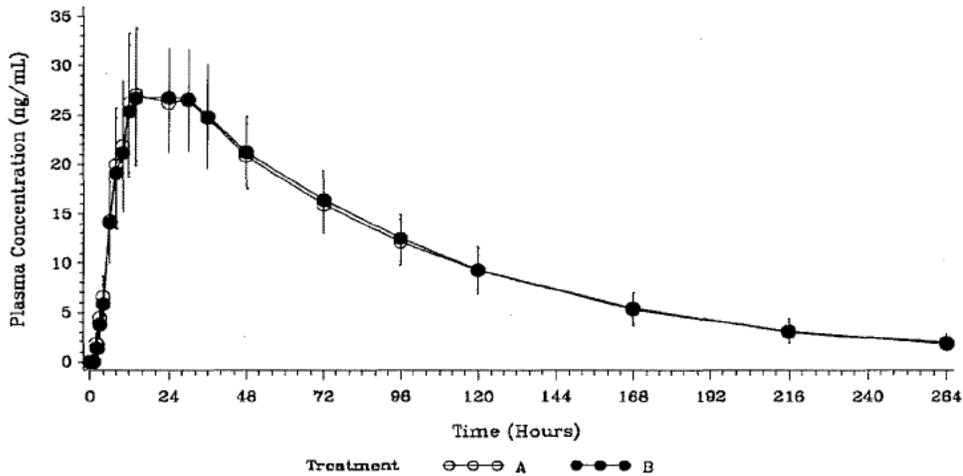
The Applicant calculated the following PK parameters using standard non-compartmental methods with Phoenix WinNonlin, version 6.2.1: C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, T<sub>max</sub>, λ<sub>z</sub>, and t<sub>1/2</sub>. The ANOVA test statistic was used to compare dose-dependent PK parameters, followed by construction of 90% confidence intervals around the respective geometric means for all three analytes; SAS Version 9.1.3 was used for the statistical computations.

### 5.6. Results

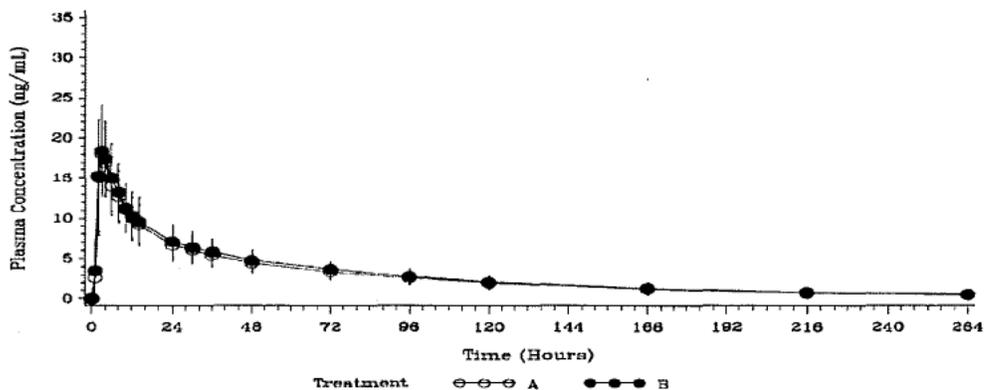
The Applicant states that 38 male and female subjects were enrolled and 31 subjects completed the study. Three individuals received one of the treatments in Period 1 but discontinued in Period 2 due to a family emergency, did not show up for Period 2, and due to a positive cotinine test at check-in for Period 2. Two subjects discontinued due to adverse events, one subject withdrew consent, while another subject was lost to follow-up.

In addition to the 7 dropouts, 8 subjects had emesis. One case of emesis (subject # 0004) occurred later than 2 times the median Tmax of donepezil but within 24 hours of drug administration; the subject was therefore included in the donepezil PK data analysis but excluded from the data set for memantine. The PK-evaluable subpopulation for memantine and donepezil were therefore 23 and 24, respectively.

The mean plasma concentration-time profiles for both treatments of each analyte are presented in Figures 6 and 7.



**Fig 6:** Mean plasma **memantine** concentration-time profiles in healthy subjects after single-dose administration of 28 mg memantine in a FDC capsule containing 28 mg memantine HCl ER (b) (4) and 10 mg donepezil HCl (b) (4) (n = 23).



**Fig 7:** Mean plasma **donepezil** concentration-time profiles in healthy subjects after single-dose administration of 10 mg donepezil HCl in a FDC capsule containing 28 mg memantine HCl ER <sup>(b) (4)</sup> and 10 mg donepezil HCl <sup>(b) (4)</sup> (n = 24).

The mean pharmacokinetic parameters and results of the statistical analyses for bioequivalence determination are provided in Tables 8 and 9 for memantine and donepezil, respectively.

**Table 8:** Statistical Summary of BE acceptance criteria for Memantine; n = 23.

<i>Parameter</i>	<i>Namenda XR + Aricept (Treatment A) Mean ± SD (n = 23)</i>	<i>MDX-8704 (Treatment B) Mean ± SD (n = 23)</i>	<i>Ratio of Geometric LS Means (B/A)</i>	<i>90% CI of the Ratio or p-Value</i>
$C_{max}$ , ng/mL	28.5 ± 6.3	28.5 ± 6.3	1.001	0.966 - 1.037
$AUC_{0-t}$ , ng•h/mL	2781.9 ± 553.2	2797.7 ± 535.6	1.009	0.977 - 1.042
$AUC_{0-\infty}$ , ng•h/mL	2966.0 ± 642.7	2966.0 ± 609.2	1.004	0.970 - 1.040
$T_{max}$ , h <sup>a</sup>	14.0 (12.0, 36.0)	24.0 (12.0, 36.1)	1.08 <sup>b</sup>	0.268 <sup>c</sup>
$T_{1/2}$ , h	61.8 ± 9.3	60.1 ± 8.8	—	—

**Table 9:** Statistical Summary of BE acceptance criteria for Donepezil; n = 24.

<i>Parameter</i>	<i>Namenda XR + Aricept (Treatment A) Mean ± SD (n = 24)</i>	<i>MDX-8704 (Treatment B) Mean ± SD (n = 24)</i>	<i>Ratio of Geometric LS Means (B/A)</i>	<i>90% CI of the Ratio or p-Value</i>
$C_{max}$ , ng/mL	19.3 ± 5.5	19.1 ± 5.3	0.987	0.933 - 1.043
$AUC_{0-t}$ , ng•h/mL	747.9 ± 227.0	791.3 ± 229.8	1.060	1.037 - 1.084
$AUC_{0-\infty}$ , ng•h/mL	837.9 ± 278.1	880.6 ± 268.7	1.055	1.033 - 1.077
$T_{max}$ , h <sup>a</sup>	3.00 (2.00, 4.05)	3.00 (2.00, 6.00)	1.01 <sup>b</sup>	> 0.999 <sup>c</sup>
$T_{1/2}$ , h	68.8 ± 24.0	68.5 ± 21.4	—	—

The geometric 90 % confidence intervals were within 80 – 125 % for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . The Applicant concludes that memantine and donepezil in the FDC capsules are bioequivalent to their respective single-entity reference products.

### 5.7. Reviewer's Assessment of BE Study: PENDING

This Reviewer confirmed the BE statistical results provided by the Applicant using SAS version 9.3. Therefore, BE study MDX-PK-104 is acceptable, provided the report from OSI, which is currently pending for the bioanalytical site does not identify any issues for this BE study.

## 6. VALIDITY OF THE IVIVC MODEL

The two biowaiver requests in this NDA rely in part on the IVIVC established for the single-entity memantine HCl ER capsules in NDA 22525, which was approved in 2010. In order to apply the established model to the memantine component of the FDC capsules in this NDA (206439) to support the biowaiver requests, the model must be cross-validated; in other words, the predicted memantine  $AUC_t$  and  $C_{max}$  for the FDC product must be within 20% of the observed parameters for the clinical batch in NDA 22525. Although the Applicant did not address the model validity in the submission, the review team compared the predicted memantine PK parameters for the higher strength of the FDC (28/10 mg) to those for the target (clinical batch) in NDA 22525.

**Table 10: IVIVC-predicted and observed memantine AUC and  $C_{max}$  for the FDC capsules (28/10 mg) and the observed PK parameters for the target single-entity product in NDA 22525.**

PK Parameter	Predicted <sup>a</sup> FDC, 28/10 mg	Observed <sup>b</sup> FDC, 28/10 mg	Observed <sup>c</sup> Namenda XR, 28 mg (NDA 22525)
$C_{max}$ , ng/mL	30.75	28.5 ± 6.3	29.4 ± 5.1
$AUC_t$ , ng*h/mL	2982.65	2797.7 ± 553	2619.7 ± 533
$AUC_{\infty}$ , ng*h/mL	3123.12	2966 ± 609	2766.6 ± 597

a = data from page 17 in [\cdsesub1\evsprod\nda206439\0000\m1\us\in-vivo-study-waiver-request.pdf](#)

b = data from page 4 in [\cdsesub1\evsprod\nda206439\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\mdx-pk-104\mdx-pk-104.pdf](#)

c = data from page 24 in [\cdsesub1\evsprod\nda022525\0000\m2\27-clin-sum\summary-biopharm.pdf](#)

The IVIVC-predicted FDC:Observed Namenda XR ratios for  $C_{max}$ ,  $AUC_t$ , and  $AUC_{\infty}$  are 104.59, 113.85, and 112.89 %, respectively. The corresponding ratios for the Observed FDC: Observed Namenda XR are 96.94, 106.79, and 107.21, respectively. Since all ratios are within 20% of the target single-entity product, application of the IVIVC model is adequately supported and therefore it is considered valid for the memantine component of the FDC product.

## 7. BIOWAIVER REQUESTS

The Applicant submitted two biowaiver requests: (i) site change for (b) (4) of the two active components from Forest Research Institute, Commack, NY (Clinical batch) to Forest Laboratories, Ireland (Commercial batches); (ii) the requirement for an in-vivo bioavailability study on the lower strength of the FDC product, 14/10 mg(Memantine HCl/donepezil HCl).

### 7.1. Biowaiver for Site change (from NY to Ireland)

The clinical and registration batches of the proposed FDC product were manufactured in Commack, NY but the commercial product will be manufactured in Ireland. The SUPAC-MR guidance classifies this as a Level 3 change which requires a bioequivalence study. Per the pre-NDA meeting discussions, the Applicant submitted a Comparability Protocol and results of comparative dissolution tests for the donepezil component. In addition, the approved IVIVC was used by the Applicant to support the biowaiver for the memantine component. The supporting data and dissolution profile comparisons can be located at <\\cdsesub1\evsprod\nda206439\0000\m3\32-body-data\32r-reg-info\comparability-protocol-manufacturing-sites.pdf>.

#### 7.1.1. Donepezil HCl

In order to demonstrate the similarity in donepezil release rate from the FDC capsules manufactured at the clinical and commercial sites, the Applicant carried out dissolution tests using media at pH 1.2, 4.5 and 6.8. As shown in Tables 11 and 12, the results are similar between the two sites at all sampling time points and for both the high (28/10 mg) and low (14/10 mg) strengths.

**Table 11: Mean donepezil dissolution data for Memantine HCl/Donepezil HCl ER Capsules, 28/10 mg manufactured at Clinical and Commercial sites (batch 1118755; n = 12)**

Time point (min)	pH = 1.2	pH = 4.5	pH = 6.8
10	102	96	99
20	104	102	100
30	104	102	100
40	104	102	100
60	104	102	101

**Table 12: Mean donepezil dissolution data for Memantine HCl/Donepezil HCl ER Capsules, 14/10 mg manufactured at Clinical and Commercial sites (batch 1118758; n = 12)**

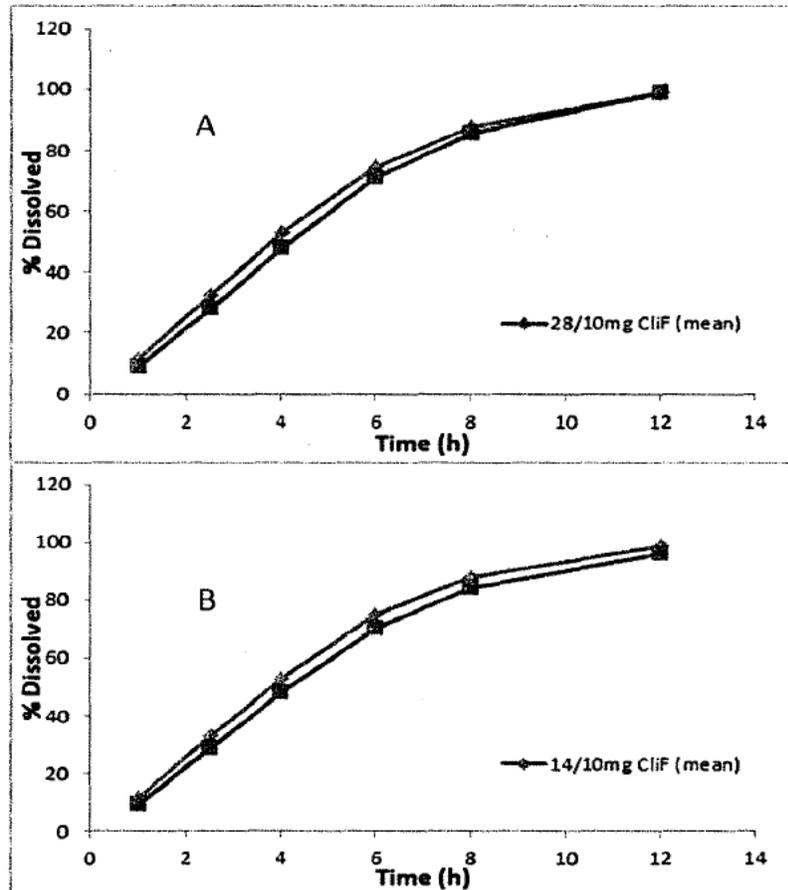
Time point (min)	pH = 1.2	pH = 4.5	pH = 6.8
10	101	97	91
20	102	100	99
30	102	100	99
40	102	100	99
60	102	100	100

As stated earlier in section 3.1, more than  $\frac{90}{40}$ % donepezil is released in 10 – 20 min from the registration/stability batches at all storage conditions over 12 months.

#### 7.1.2. Memantine HCl

The proposed dissolution method was used to generate memantine multipoint dissolution profile comparisons of batches manufactured at the clinical and commercial sites; the Applicant manufactured three batches of each strength of the proposed FDC product. As

depicted in Figure 8, the dissolution profiles of the product made at the two sites are similar. The  $f_2$  similarity test results among the batches of each strength ranged from 67 to 83. It should be noted that the choice of the references is inappropriate; since use of the correct approach for the references will not change the outcome of the  $f_2$  similarity test, an IR was not sent to the Applicant.



Clif = clinical formulation; ComF = commercial formulation.

**Figure 8: Grand mean memantine dissolution profiles of Memantine HCl/Donepezil HCl FDC Extended-Release Capsules, 28/10 mg (3 batches per site; upper panel, A) and 14/10 mg (3 batches per site; lower panel, B).**

The additional supportive data for the site change biowaiver request was obtained from the approved IVIVC model established for the single-entity product, Memantine HCl ER Capsules. Since the same extended-release memantine <sup>(b) (4)</sup> are contained in the FDC capsules, the Applicant used the IVIVC model to predict memantine  $C_{max}$  and AUCs for the product batches manufactured at the two sites. The predicted grand mean memantine plasma concentration-time curves for the two sites are virtually superimposable for both the 28/10 and 14/10 mg strengths; the PK parameter prediction results are summarized in Tables 13 (14/10 mg) and 14 (28/10 mg).

**Table 13: Predicted grand mean memantine PK parameters for Memantine HCl/Donepezil HCl FDC Extended-Release Capsules, 14/10 mg using the approved IVIVC model and in-vitro dissolution data; n = 3 batches per site.**

Parameter	14 mg/10 mg, N = 3 (Clinical Site Batch, Reference)		14 mg/10 mg, N = 3 (Commercial Site Batch)		% of Deviation
	Predicted	CV (%)	Predicted	CV (%)	
C <sub>max</sub> (ng/mL)	15.23	1.20	14.78	0.80	-2.96
AUC <sub>0-t</sub> (h*ng/mL)	1491.99	1.00	1452.63	0.50	-2.64
AUC <sub>0-∞</sub> (h*ng/mL)	1562.45	1.10	1521.81	0.50	-2.60

**Table 14: Predicted grand mean memantine PK parameters for Memantine HCl/Donepezil HCl FDC Extended-Release Capsules, 28/10 mg using the approved IVIVC model and in-vitro dissolution data; n = 3 batches per site.**

Parameter	28 mg/10 mg, N = 3 (Clinical Site Batches, Reference)		28 mg/10 mg, N = 3 (Commercial Site Batches)		% of Deviation
	Predicted	CV (%)	Predicted	CV (%)	
C <sub>max</sub> (ng/mL)	30.37	1.10	30.18	1.70	-0.60
AUC <sub>0-t</sub> (h*ng/mL)	2983.63	0.00	2975.47	1.60	-0.27
AUC <sub>0-∞</sub> (h*ng/mL)	3124.69	0.10	3117.68	1.60	-0.22

### **Reviewer's Assessment: SATISFACTORY**

*The Applicant's supporting data for the manufacturing site change biowaiver request are adequate; the request for a waiver of bioavailability study on the proposed drug product manufactured at the clinical and commercial sites is therefore granted.*

## **7.2. Biowaiver for 14/10 mg strength of the FDC capsule**

The Applicant conducted a bioequivalence study (No. MDS-PK-104) on the highest strength (28/10 mg; memantine HC/donepezil HCl) of the FDC product and submitted a biowaiver request for the lower strength (14/10 mg). The Applicant's supporting data are assessed in this section of the review.

### **7.2.1. Donepezil HCl**

On the basis of regulatory science advice the Applicant received from the Agency in meetings during the IND stage, including the pre-NDA meeting, a BCS (b) (4) designation package for donepezil was submitted to the IND (# 109763). The assessment of the data package submitted to IND 109763 was posted in DARRTS by this Reviewer on 7/9/2014 and concluded as follows:



The Applicant’s data on donepezil supports the use of in-vitro dissolution data in lieu of an in-vivo bioavailability study. The percent donepezil released from the 14/10 mg strength (lot # BN00023907) was identical to the 28/10 mg clinical batch (lot # BN00023559) at pH 1.2, pH 4.5, and pH 6.8. The results are summarized in Table 15

**Table 15: Comparative mean donepezil dissolution (n = 12) from Memantine HCl /Donepezil HCl ER FDC Capsules, 14/10 mg (lot # BN00023907) and 28/10 mg lot # BN00023559); USP1, 100 rpm.**

Time (min)	pH = 1.2 HCl/NaCl Buffer		pH = 4.5 Acetate Buffer		pH = 6.8 Phosphate Buffer	
	28 mg/10 mg (Reference)	14 mg/10 mg (Test)	28 mg/10 mg (Reference)	14 mg/10 mg (Test)	28 mg/10 mg (Reference)	14 mg/10 mg (Test)
10	98	99	103	100	86	96
20	101	100	104	102	100	98
30	101	100	105	102	100	98
40	101	100	106	102	101	98
60	101	100	106	102	101	98
f2 Value	Not applicable due to rapid dissolution					

**7.2.2. Memantine HCl**

The Applicant used the approved IVIVC model for the single-entity memantine HCl product to accurately predict the in-vivo memantine exposure for the clinical batch of the FDC product (28/10 mg, # BN00023559); the predicted and observed memantine AUC and C<sub>max</sub> were similar. Results of in-vitro dissolution comparisons (14/10 mg versus 28/10 mg) in the proposed regulatory method and in 2 additional pH media can therefore be assessed in lieu of an in-vivo study on the lower strength.

Similar to the Donepezil component, the dissolution of the lower strength (14/10 mg) was identical to the highest strength (28/10 mg) in all three dissolution media; the results were confirmed by the f2 Similarity test. The f2 values obtained in media at pH 1.2, 4.5, and 6.8 were 100, 81 and 80, respectively (Table 16).

**Table 16: Memantine comparative multi-media dissolution profiles from Memantine HCl /Donepezil HCl ER FDC Capsules, 14/10 mg (lot # BN00023907) and 28/10 mg lot # BN00023559); USP1, 100 rpm.**

Time (h)	pH 1.2, 0.1N HCl/NaCl				pH 4.5, Acetate Buffer				pH 6.8, Phosphate buffer			
	FDC 28 mg/10 mg (Reference)	Namenda XR 14 mg*	Namenda XR 14 mg + Aricept 10 mg	FDC 14 mg/10 mg	FDC 28 mg/10 mg (Reference)	Namenda XR 14 mg	Namenda XR 14 mg + Aricept 10 mg	FDC 14 mg/10 mg	FDC 28 mg/10 mg (Reference)	Namenda XR 14 mg	Namenda XR 14 mg + Aricept 10 mg	FDC 14 mg/10 mg
1	11	10	9	11	12	11	11	12	12	11	10	11
2.5	32	NA	27	32	40	33	32	40	37	32	31	35
4	54	49	45	54	67	56	55	66	61	53	53	58
6	76	NA	67	76	89	81	80	87	82	76	76	79
8	89	86	82	89	98	94	93	95	92	89	90	90
12	99	98	97	99	103	102	102	99	100	100	100	98
F2	Reference	75	60	100	Reference	59	57	81	Reference	66	65	80

\*Data taken from CoA as part of commercial release testing. F2 value is calculated based on 1, 4, 8 and 12 h timepoints

**Reviewer's Assessment: SATISFACTORY**

Both active components in the high strength of Memantine HCl /Donepezil HCl ER FDC Capsules, 28/10 mg were shown to be bioequivalent to their respective individual components in study MDX-PK-104. In addition, the Applicant's comparative dissolution data for the low (14/28 mg) and high (28/10 mg) strengths of the FDC product have been demonstrated to be similar. The request for a waiver of bioavailability study on the lower strength is therefore granted.

## 8. RISK EVALUATION

The risk assessment evaluation for the dissolution CQA component and the dose dumping effect of the formulation in the presence of alcohol on Memantine HCl ER/Donepezil Capsules is presented in Table 17. Please see the CMC review for the other CQAs.

**Table 17: Final Risk Assessment of Memantine HCl ER/Donepezil FDC Capsules**

From Initial Quality Assessment			Review Assessment			
Product attribute/CQA	Factors that can impact the CQA	Risk Ranking*	Risk approach	Mitigation	Risk Evaluation	Lifecycle Considerations/Comments**
Dissolution Donepezil	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	Low	(b) (4) The dissolution profile of the donepezil (b) (4) should meet specification due to its high solubility and the (b) (4)		Acceptable	No comments since donepezil is (b) (4) dissolving, is highly soluble and highly permeable.
Dissolution Memantine	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials (rate controlling polymers)</li> <li>API sources</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	Medium	The drug (b) (4) product will be packaged in HDPE bottles. (b) (4)		Acceptable	-Adhere to SUPAC-MR guidelines for minor and major changes. -For changes in the container closure system, adequate stability/dissolution data should be evaluated due to potential effect on release rate.
Alcohol Dose Dumping	<ul style="list-style-type: none"> <li>Formulation</li> <li>Process parameters</li> <li>Scale/equipment</li> <li>Site</li> </ul>	High	Even though the product has a pronounced effect in dose dumping with 40% alcohol, clinical trials suggested that the adverse events were mild for doses up to 100mg		Acceptable	Change in formulation requires evaluating potential alcohol dose dumping.

\*Risk ranking applies to product attribute/CQA

\*\*For example, post marketing commitment, knowledge management post approval, etc.

**Reviewer's Assessment: SATISFACTORY**

**Okponanabof  
a Eradiri, Ph.D.**

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