

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206439Orig1s000**

**MEDICAL REVIEW(S)**

## Review and Evaluation of Clinical Data

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<b>NDA</b>	<b>206439</b>
<b>Sponsor:</b>	<b>Forest</b>
<b>Drug:</b>	<b>MDX-8704</b>
<b>Proposed Indication:</b>	<b>Alzheimer's Disease</b>
<b>Material Submitted:</b>	<b>New Drug Application</b>
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<b>Reviewer:</b>	<b>Ranjit B. Mani, M.D.</b>

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## EXECUTIVE SUMMARY

### ***Recommendation***

I recommend that MDX-8704 (NAMZARIC), a fixed-dose combination drug product (capsule) consisting of extended-release memantine hydrochloride and donepezil hydrochloride, be approved for the treatment of moderate to severe dementia of the Alzheimer's type.

### ***Proposed Indication***

This New Drug Application (NDA) seeks the approval of MDX-8704 (NAMZARIC) for the treatment of moderate to severe dementia of the Alzheimer's type.

### ***Summary Of Clinical And Nonclinical Findings***

In this application, the sponsor seeks the approval of two strengths of MDX-8704 (NAMZARIC), a fixed-dose combination drug, for the treatment of moderate to severe dementia of the Alzheimer's type (Alzheimer's Disease): extended-release memantine in a dose of 28 mg combined with donepezil in a dose of 10 mg (also referred to as the 28 mg/10 mg strength); and extended-release memantine in a dose of 14 mg combined with donepezil in a dose of 10 mg (also referred to as the 14 mg/10 mg strength). Each of the above strengths of this product is intended for once daily administration.

Memantine hydrochloride is currently marketed in this country under the brand name NAMENDA for the treatment of moderate to severe dementia of the Alzheimer's type, by the sponsor of the current application. Several formulations of NAMENDA are approved for that indication, including an extended-release capsule (NAMENDA XR; 7 mg, 14 mg, 21 mg, and 28 mg strengths) which is to be administered once daily. Donepezil hydrochloride (ARICEPT [Eisai] and several generic formulations) is currently marketed in this country for the treatment of mild, moderate, and severe dementia of the Alzheimer's type; several strengths and formulations of donepezil hydrochloride are marketed, including a 10 mg tablet approved for mild, moderate, and severe Alzheimer's Disease.

This application has been submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act and relies primarily on the following to support the approval of the current NDA: clinical pharmacology (bioequivalence and bioavailability) studies of the proposed fixed-dose combination product which are described in full in this submission; NDA 21487 for NAMENDA and NDA 22525 for NAMENDA XR (by cross-reference); and the Agency's finding of safety and effectiveness for ARICEPT (under NDA 20690 submitted by Eisai). The sponsor asserts that the safety and efficacy of the fixed-dose combination of extended-release memantine hydrochloride and donepezil hydrochloride is supported by

the Agency's approval of both components of the fixed-dose combination and the additional data provided in the current application. Agreement had been reached between the sponsor and Agency in advance of the submission of this application regarding the currently proposed basis for the approval of MDX-8704 (NAMZARIC) for the treatment of moderate to severe dementia of the Alzheimer's type prior to the submission of this application.

The combination MDX-8704 drug product (capsule) uses the same extended-release memantine (b) (4) used in NAMENDA XR capsules.

The new clinical data contained in this submission consist of complete reports of the following clinical pharmacology studies.

- MDX-PK-104, a randomized, open-label, single-dose, two-way crossover study intended to evaluate the bioequivalence of the memantine extended-release and donepezil components of MDX-8704 (using the product containing 28 mg of extended-release memantine and 10 mg of donepezil) with those of co-administered NAMENDA XR 28 mg and donepezil 10 mg. This study was conducted in 38 healthy men and women, aged 18 to 45 years.
- MDX-PK-105, a randomized, open-label, single-dose, three-way crossover study intended to evaluate the effect of food and the effect of sprinkling the capsule contents on applesauce on the relative bioavailability of memantine and donepezil after the oral administration of MDX-8704 (using the product containing 28 mg of extended-release memantine and 10 mg of donepezil). This study was conducted in 36 healthy men and women, aged 18 to 45 years.

Safety assessments in the above studies included the assessment of adverse events, vital signs, electrocardiograms, safety laboratory tests, and suicidality; and physical examinations. A detailed review of the safety data for both studies yielded no findings of clinical concern.

The pharmacokinetic results of the above studies demonstrated the following:

- The bioequivalence of both memantine and donepezil whether administered as a 28 mg capsule of NAMENDA XR with a 10 mg tablet of donepezil or as the fixed-dose combination 28 mg/10 mg capsule.
- Food had no clinically meaningful effect on the bioavailability of the MDX-8704 28 mg/10 mg capsule. The capsule was bioequivalent whether administered as an intact capsule or as capsule contents sprinkled in apple sauce.

Biopharmaceutics data in this submission included *in vitro* dissolution profiles for both strengths of MDX-8704, an *in vitro* alcohol dose dumping study, and *in vivo in vitro* correlation for the extend-release memantine component of MDX-8704.

### ***Conclusions Of Other Review Disciplines***

The Pharmacology –Toxicology, Clinical Pharmacology, Chemistry, and Biopharmaceutics review staff each concluded that this application was approvable, while recommending changes to the submitted Prescribing Information. Several other Agency offices contributed to editing the text of the Prescribing Information and Patient Package Insert.

### ***Overall Conclusion***

This New Drug Application provides substantial evidence for the efficacy and safety of MDX-8704 (NAMZARIC), a fixed-dose combination drug product (capsule) consisting of extended-release memantine hydrochloride and donepezil hydrochloride for the treatment of moderate to severe dementia of the Alzheimer's type.

## 1. Background

This New Drug Application (NDA) seeks the approval of MDX-8704, a fixed-dose combination drug product (capsule) containing extended-release memantine hydrochloride and donepezil hydrochloride as components, for the treatment of moderate to severe dementia of the Alzheimer's type (i.e., Alzheimer's Disease).

The sponsor seeks the approval of following two strengths of MDX-8704 for that indication.

- Extended-release memantine in a dose of 28 mg combined with donepezil in a dose of 10 mg (also referred to in this submission as the 28/10 mg strength).
- Extended-release memantine in a dose of 14 mg combined with donepezil in a dose of 10 mg (also referred to in this submission as the 14/10 mg strength).

Each of the above strengths of MDX-8704 is intended for administration once daily.

Memantine is currently marketed in this country under the brand name Namenda® (Forest Laboratories). Formulations of Namenda® that are currently marketed include tablets (5 mg and 10 mg), an oral solution (2 mg/mL) and an extended-release capsule (Namenda XR®; 7 mg, 14 mg, 21 mg, and 28 mg strengths). All formulations of Namenda® are approved for the treatment of moderate to severe Alzheimer's Disease. Namenda XR® is to be taken once daily whereas tablet and oral solution formulations of Namenda® are to be taken twice daily. NDA numbers for the various approved formulations of Namenda® are: 21487 (for the 5 mg and 10 mg tablet formulations), 21627 (for the oral solution formulation), and 22525 (for Namenda XR®). The current product is to use the memantine hydrochloride extended-release (b) (4) contained in Namenda XR® 14 mg and 28 mg capsules as its extended-release memantine component.

Donepezil is currently marketed in this country under the brand name Aricept® [Eisai] as a tablet (in 5 mg, 10 mg, and 23 mg strengths) and as an orally-disintegrating tablet (in 5 mg and 10 mg strengths). The 5 mg and 10 mg strengths of the tablet and orally-disintegrating tablet formulations are currently approved for the treatment of mild to moderate Alzheimer's Disease. The 10 mg strengths of the tablet and orally-disintegrated tablet formulations, and the 23 mg strength of the tablet formulation are approved for the treatment of moderate to severe Alzheimer's Disease. An oral solution formulation of Aricept® is also approved in this country, but has never been marketed. NDA numbers for the various approved formulations of Aricept® are as follows: 20690 (for the 5 mg and 10 mg tablet strengths); 21719 (for the oral solution formulation); 21720 (for the 5 mg and 10 mg orally-disintegrating tablet strengths); and 22568 (for the 23 mg tablet formulation). Generic formulations of donepezil are also marketed in this country. All formulations of donepezil are to be administered once daily.

This application has been submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The sponsor relies primarily on the following to support the approval of the current NDA.

- Clinical pharmacology (bioequivalence and bioavailability) studies of the proposed fixed-dose combination product, i.e., Studies MDX-PK-104 and MDX-PK-105, which are described in full in this submission.
- NDA 21487 for Namenda® and NDA 22525 for Namenda XR® (by cross-reference).
- The Agency's finding of safety and effectiveness for Aricept® (under NDA 20690, submitted by Eisai).

The sponsor asserts that the safety and efficacy of the fixed-dose combination of extended-release memantine hydrochloride and donepezil hydrochloride is supported by the Agency's approval of both components of the fixed-dose combination and the additional data provided in the current application.

The extended-release memantine and donepezil combination product for which the sponsor is seeking approval under the current application has been developed under IND 109763, originally submitted on September 13, 2010, to which the current application is also cross-referenced. While under development, this combination product has been referred to first as "ADS-8704," and then as "MDX-8704." The name "MDX-8704" is also used in this review to refer to the fixed-dose combination drug product consisting of extended-release memantine hydrochloride and donepezil hydrochloride.

The proprietary name "NAMZARIC" has been proposed by the sponsor for the proposed fixed-dose combination of extended-release memantine hydrochloride and donepezil hydrochloride.

Note that the name "memantine," when used at any place in this review, refers to memantine hydrochloride. Likewise, the name "donepezil," when used at any place in this review, refers to donepezil hydrochloride.

**This document is intended to serve simultaneously a primary clinical review, a Team Leader review, and a Cross-Disciplinary Team Leader review.**

## **2. Contents Of Submission**

This NDA has been submitted in standard electronic Common Technical Document format. The application thus has 5 main sections, enumerated as listed below.

1. Regional.
2. Common Technical Document summaries.
3. Quality.
4. Nonclinical study reports.

## 5. Clinical study reports.

Note that Section 5 of this application contains the complete study reports of the following 4 clinical studies.

- MDX-PK-104.
- MDX-PK-105.
- MEM-PK-13.
- MEM-PK-07.

## 3. Contents Of Review

The contents of this application have been reviewed using the following primary headings in the same consecutive order as below.

- History of development of proposed new fixed-dose combination drug product.
- Description of proposed new fixed-dose combination drug product.
- Clinical data.
- Summary of clinical pharmacology.
- Summary of biopharmaceutics.
- Summary of reviews by other Agency disciplines.
- Labeling.
- Financial disclosure certification.
- Pediatric waiver request.
- Overall conclusions.
- Recommendation.

## 4. History Of Development Of Proposed New Fixed-Dose Combination Drug Product

### 4.1 Rationale For Development Of Formulation

The rationale for the sponsor's development of the fixed-dose combination product under review may briefly be summarized as follows.

- Currently, the American Association of Geriatric Psychiatrists recommends the treatment of mild Alzheimer's Disease with an acetylcholinesterase inhibitor, with the addition of memantine when the disease worsens to the moderate phase. Other experts have made similar recommendations.
- About 70% of all memantine use is in combination with an acetylcholinesterase inhibitor, with donepezil accounting for a further 70% of all memantine use as part of such a combination.
- MDX-8704, administered once daily, will simplify the administration of memantine and donepezil in combination. The formulation also provides for the sprinkling of the contents of the capsule on soft foods if needed, thereby also facilitating its

administration. The expectation is that the use of MDX-8704 will lead to greater compliance and adherence to treatment, as well as a better therapeutic outcome.

#### **4.2 Interactions Between Sponsor And Agency Regarding Development Of Formulation**

The development of this fixed-dose combination formulation of extended-release memantine and donepezil has been the subject of the following interactions between the Agency and sponsor, all of which were subsumed under IND 109763.

- An End-of-Phase 2 Meeting held on October 13, 2011 (with representatives of Adamas Pharmaceuticals who were developing this fixed-dose combination at that time).
- A Type C Meeting held on June 20, 2013 (with representatives of both Adamas Pharmaceuticals and Forest Laboratories).
- Aa Pre-NDA Meeting held on November 19, 2013 (with representatives both Adamas Pharmaceuticals and Forest Laboratories).

Please see the Minutes of each of the above meetings for full details of the discussion at each. However, the following agreements reached in the course of those meetings are especially noteworthy, from a purely clinical perspective.

- It was agreed that no additional studies of the efficacy of the fixed-dose combination of memantine extended-release and donepezil would be required. The Agency agreed that the efficacy of the co-administration of memantine and donepezil had already been sufficiently evaluated in two studies previously reviewed by the Agency: those were Study MEM-MD-02 submitted and fully reviewed under NDA 21487, and Study MEM-MD-50 submitted and fully reviewed under NDA 22525.
- It was also agreed that the conduct of two further clinical pharmacology studies, would be sufficient to support the approval of the proposed fixed-dose combination of extended-release memantine and donepezil:
  - MDX-PK-104, a randomized, open-label, single-dose, two-way crossover study intended to evaluate the bioequivalence of the memantine extended-release and donepezil components of MDX-8704 (using the strength containing 28 mg of extended-release memantine and 10 mg of donepezil) with those of co-administered Namenda XR<sup>®</sup> 28 mg and donepezil 10 mg.
  - MDX-PK-105, a randomized, open-label, single-dose, three-way crossover study intended to evaluate the effect of food and the effect of sprinkling the capsule contents on applesauce on the relative bioavailability of memantine and donepezil after the oral administration of MDX-8704 (using the strength containing 28 mg of extended-release memantine and 10 mg of donepezil).

An *in vitro* alcohol dose dumping study of the fixed-dose combination product was also to be conducted.

- It was also agreed that the proposed strengths of the fixed-dose combination product (to which this application pertains) were appropriate for use in patients already being treated with the combination of donepezil and extended-release memantine administered as separate products, but at the same dosage.

Note that in the Briefing Package for the End-of-Phase 2 Meeting held on October 13, 2011, and in later submissions, the sponsor had repeatedly indicated an intention to submit a 505(b)(2) NDA for MDX-8704: it was stated at those times that the proposed NDA was to reference the efficacy and safety data for NDA 22525 (for Namenda XR<sup>®</sup>), NDA 21487 (for Namenda<sup>®</sup> tablets and Namenda<sup>®</sup> oral solution), and NDA 20690 (for Aricept<sup>®</sup> tablets).

## **5. Description Of Proposed New Fixed-Dose Combination Drug Product**

As stated by the sponsor in this application:

- The combination MDX-8704 drug product uses the same extended-release memantine <sup>(b) (4)</sup> used in Namenda XR<sup>®</sup> capsules.
- The 14 mg/10 mg MDX-8704 product is a locked, Size 2, light green opaque capsule with a black 'FL 14/10' radial imprint on the capsule.
- The 28 mg/10 mg MDX-8704 product is a locked, Size 1, blue opaque capsule with a black 'FL 14/10' radial imprint on the capsule.

The components and quantitative composition of the two strengths of MDX-8704 proposed for marketing are summarized in the following table, which I have copied from the submission.

Component	Function	Quality Standard	Unit Dose Composition			
			14 mg/10 mg		28 mg/10 mg	
			(% w/w)	mg/capsule	(% w/w)	mg/capsule
(b) (4)						
Memantine HCl	Drug substance	In-house	7.4	14	10.1	28
Povidone (b) (4) USP		(b) (4)				(b) (4)
Talc, USP						
Sugar spheres (b) (4) NF		(b) (4)				
Donepezil HCl, USP			5.3	10	3.6	10
Lactose monohydrate, NF						(b) (4)
Microcrystalline cellulose, NF						
Corn starch, NF						
Colloidal silicon dioxide, NF						
Magnesium stearate, NF						
<b>Total filled weight</b>						
Empty gelatin capsule, size 2						
Empty gelatin capsule, size 1						
<b>Total Theoretical Memantine HCl ER/Donepezil HCl Capsules</b>			----	249.9	----	353.9
						(b) (4)

## 6. Clinical Data

### 6.1 Introduction

The efficacy of the fixed-dose combination drug product consisting of extended-release memantine hydrochloride and donepezil hydrochloride (MDX-8704) as a treatment for moderate to severe dementia of the Alzheimer's type was established by demonstrating the bioequivalence of MDX-8704 with co-administered memantine hydrochloride extended-release and donepezil hydrochloride.

Accordingly, the clinical pharmacology study that established the bioequivalence noted above and other supportive clinical pharmacology studies are described in this section, with the focus being on safety data for the two principal clinical pharmacology studies unique to this application.

### 6.2 Tabular Summary For All Clinical Studies For Which Data Has Been Included In This Application

The reports of four clinical pharmacology studies have been included in this submission. Those clinical studies have been summarized in the following table, which has been copied from the current submission.

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration</i>	<i>Number of Subjects</i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment</i>
BE	MDX-PK-104	5.3.1.2	To establish bioequivalence of memantine and donepezil after a single oral dose of MDX-8704 versus coadministered Namenda XR and Aricept	Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose study; no control	(1) MDX-8704 Capsule (memantineHCl ER/donepezil HCl, 28/10 mg); (2) Namenda XR Capsule, 28 mg; (3) Aricept Tablet, 10 mg <b>Treatment A:</b> Single oral dose of a 28-mg Namenda XR capsule and a 10-mg Aricept tablet coadministered under fasted conditions <b>Treatment B:</b> Single oral dose of MDX-8704 (memantine ER and donepezil 28 mg/10 mg capsule) under fasted conditions	38	Healthy subjects	1 day in each of 2 treatment periods, separated by 21 days
Food Effect and BE	MDX-PK-105	5.3.1.1	To evaluate: (a) the effect of food on the relative bioavailability of memantine and donepezil after oral administration of an intact MDX 8704 capsule; and (b) 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	Phase 1, single-center, randomized, open-label, 3-way crossover, single-dose study; no control	MDX-8704 Capsule (memantine HCl ER/donepezil HCl, 28/10 mg) <b>Treatment A:</b> Single oral 28 mg/10 mg dose of MDX-8704 (memantine ER/donepezil capsule) administered as an intact capsule under fasting conditions <b>Treatment B:</b> Single oral 28 mg/10 mg dose of MDX-8704 (memantine ER/donepezil capsule) administered as an intact capsule following a high-fat breakfast <b>Treatment C:</b> Single oral 28 mg/10 mg dose of MDX-8704 (memantine ER/donepezil capsule) administered as capsule contents sprinkled on 30 mL of applesauce under fasting conditions	36	Healthy subjects	1 day in each of 3 treatment periods, separated by 21 days

<i>Type of Study</i>	<i>Study Identifier</i>	<i>Module Location of Study Report</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dose Regimen; Route of Administration</i>	<i>Number of Subjects</i>	<i>Healthy Subjects or Diagnosis of Patients</i>	<i>Duration of Treatment</i>
BA	MEM-PK-13*	5.3.1.1	To compare the bioavailability of three memantine HCl ER capsules with that of an IR tablet	Phase 1, single-center, randomized, open-label, 4-way crossover, single-dose study; no control	20 mg memantine IR tablet; 40 mg memantine ER capsule formulation I; 40 mg memantine ER capsule formulation II; 40 mg memantine ERcapsule formulation III <b>Treatment A:</b> Single dose of a 2 x 20-mg memantine tablet (IR) <b>Treatment B:</b> Single dose of a 40-mg memantine capsule, ER Formulation I <b>Treatment C:</b> Single dose of a 40-mg memantine capsule, ER Formulation II; <b>Treatment D:</b> Single dose of a 40-mg memantine capsule, ER Formulation III	24	Healthy subjects	1 day for each of 4 treatments separated by 21 days
PK-DDI	MEM-PK-07*	5.3.3.4	(a) to determine if there is an in vivo PK interaction between memantine and donepezil and (b) to evaluate whether coadministered memantine affected inhibition of acetylcholinesterase (AChE) activity due to donepezil	Phase 1, single-center, randomized, open-label, multiple-dose study; no control	10 mg memantine IR tablet; 5 mg Aricept tablet <b>Treatment:</b> 10-mg memantine IR tablet on Study Day 1 followed by a 14-day washout period. Beginning on Day 15, subjects took one 5-mg Aricept tablet once daily for 7 days. Beginning on Day 22, subjects took two 5-mg Aricept tablets (10 mg) once daily for 22 days. On Day 43, the subjects received a 10-mg memantine tablet concomitantly with the last dose of 10 mg donepezil	24	Healthy subjects	1 day memantine; 14 days washout, 7 days Aricept (5 mg), 22 days Aricept (2 x 5 mg), 1 day memantine (10 mg) and donepezil (10 mg)

\* CSR is included in this NDA and datasets of the study have been provided in NDA 22-525 for MEM-PK-13 and NDA 21-487 for MEM-PK-07.  
 BA = bioavailability, BE = bioequivalence; ER = extended release; IR = immediate release; HCl = hydrochloride, PK = pharmacokinetic, XR = extended release.

The above table is self-explanatory.

The complete reports of Studies MDX-PK-104 and MDX-PK-105 are unique to the current application, i.e., they have not been submitted under a New Drug Application previously. However, the complete reports of Studies MEM-PK-07 and MEM-PK-13, while included in the current application, were previously submitted under NDA 21487 and NDA 22525, respectively, and were reviewed in detail together with the respective applications under which they were submitted.

Note that in addition to the clinical studies listed in the following table, an *in vitro* alcohol dose dumping study of the proposed fixed-dose combination product has been conducted.

### **6.3 Description Of Selected Clinical Pharmacology Studies Primarily Supporting Current Application**

As already noted, Studies MDX-PK-104 and MDX-PK-105 are unique to the current application, and are therefore reviewed here in detail; as the clinical pharmacology data for those studies has been reviewed in detail by other Agency staff, this review is focused on the safety data for those studies.

#### **6.3.1 Study MDX-PK-104**

##### *6.3.1.1 Outline Of Study Design*

This was a randomized, open-label, single-dose, two-way crossover study intended to evaluate the bioequivalence of the memantine extended-release and donepezil components of MDX-8704 (in the strength containing 28 mg of extended-release memantine and 10 mg of donepezil) with those of co-administered Namenda® XR 28 mg and Aricept® 10 mg.

The study was conducted in 38 healthy men and women, aged 18 to 45 years.

The following treatments were administered with a 21-day washout period between treatments.

Treatment A: A single oral dose of Namenda XR® 28 mg (capsule) and Aricept® 10 mg (tablet) administered at the same time under fasted conditions.

Treatment B: A single oral dose of the MDX-8704 28 mg/10 mg capsule administered under fasted conditions.

##### *6.3.1.2 Safety Results*

No deaths, serious adverse events, or severe adverse events occurred in this study. All treatment-emergent adverse events were mild to moderate in severity.

One subject in Treatment Sequence AB who received Namenda® XR and Aricept® on Day 1 of Period 1 discontinued study participation after a laceration to, and fracture of, a finger that occurred on Day 15 of Period 1. Another subject, a 19-year-old man, in Treatment Sequence AB who received Namenda® XR and Aricept® on Day 1 of Period 1 discontinued study drug after developing pre-syncope symptoms 3 hours after dosing, associated with a sitting blood pressure of 46/28 mmHg 3 hours after dosing.

The incidence of treatment-emergent adverse events that occurred in 3 or more subjects overall is in the following table, which I have copied from the submission.

<i>System Organ Class Preferred Term</i>	<i>Namenda XR + Aricept (Treatment A) (N = 36) n (%)</i>	<i>MDX-8704 (Treatment B) (N = 34) n (%)</i>	<i>All Subjects<sup>a</sup> (N = 38) n (%)</i>
<b>At least 1 TEAE</b>	<b>28 (77.78)</b>	<b>26 (76.47)</b>	<b>32 (84.21)</b>
<b>Gastrointestinal disorders</b>	<b>19 (52.78)</b>	<b>23 (67.65)</b>	<b>26 (68.42)</b>
Abdominal pain	3 (8.33)	4 (11.76)	7 (18.42)
Nausea	19 (52.78)	22 (64.71)	26 (68.42)
Vomiting	7 (19.44)	8 (23.53)	9 (23.68)
<b>General disorders and administration site conditions</b>	<b>8 (22.22)</b>	<b>7 (20.59)</b>	<b>13 (34.21)</b>
Feeling hot	2 (5.56)	6 (17.65)	8 (21.05)
Feeling of body temperature change	3 (8.33)	0	3 (7.89)
<b>Nervous system disorders</b>	<b>18 (50.00)</b>	<b>19 (55.88)</b>	<b>24 (63.16)</b>
Dizziness	13 (36.11)	14 (41.18)	20 (52.63)
Headache	5 (13.89)	4 (11.76)	6 (15.79)
Somnolence	2 (5.56)	1 (2.94)	3 (7.89)

Notes: Medical Dictionary for Regulatory Activities, Version 16.0 was used to code adverse events. Subjects were counted only once in each event category. A TEAE was assigned to the previous treatment if it occurred during a washout period. N = number of subjects in the Safety Population. n = number of subjects in the specific category. Percentages were calculated as  $100 \times (n/N)$ .

a Subjects who took any investigational product (counted only once).

Treatment A = a single oral dose of Namenda XR 28-mg capsule and Aricept 10-mg tablet co-administered under fasted conditions.

Treatment B = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28-mg/10-mg capsule administered under fasted conditions.

ER = extended release; TEAE = treatment-emergent adverse event; XR = extended release.

Note that study drug was administered without titration to all subjects participating in the study. Ordinarily (i.e., as recommended in the Prescribing Information), Namenda XR<sup>®</sup> would have been administered in a dose of 28 mg once daily only after titration over a period of 3 weeks, and donepezil would have been administered in a dose of 10 mg once daily only after titration over a minimum of 4 weeks.

There were no vital sign data of concern beyond the above. Electrocardiograms, safety laboratory tests, physical examinations, and suicidality assessments (the Columbia-Suicide Severity Rating Scale) also did not yield any data of concern.

### 6.3.1.3 Pharmacokinetic Results

The results of this study are summarized in the following tables which I have copied from the submission.

The pharmacokinetic parameters and results of the statistical analysis for memantine when study drug was administered under fasted conditions are below.

<b>Pharmacokinetic Parameters (Mean ± SD) and Statistical Analysis for Memantine—Pharmacokinetic Population</b>				
<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	—	—

Notes: A linear effects model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect was used to compare  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  between MDX-8704 (Treatment B; test) and Namenda XR + Aricept (Treatment A; reference).

a For  $T_{max}$ , the median (minimum, maximum) is presented.

b Ratio of arithmetic means.

c The Wilcoxon signed-rank test was performed to calculate the p-value.

Treatment A = a single oral dose of Namenda XR 28-mg capsule and Aricept 10-mg tablet co-administered under fasted conditions.

Treatment B = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28-mg/10-mg capsule administered under fasted conditions.

$AUC_{0-t}$  = area under the plasma concentration versus time curve from time 0 to time t;  $AUC_{0-\infty}$  = area under the plasma concentration versus time curve from time 0 to infinity;  $C_{max}$  = maximum plasma drug concentration; CI = confidence interval; ER = extended release; LS = least squares;  $T_{1/2}$  = terminal elimination half-life;  $T_{max}$  = time of maximum plasma drug concentration; XR = extended release.

The pharmacokinetic parameters and results of the statistical analysis for donepezil when study drug was administered under fasted conditions are in the next table.

<b>Pharmacokinetic Parameters (Mean ± SD) and Statistical Analysis for Donepezil—Pharmacokinetic Population</b>				
<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	—	—

Notes: A linear effects model with sequence, treatment, and period as fixed effects and subject within sequence as a random effect was used to compare  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  between MDX-8704 (Treatment B; test) and Namenda XR + Aricept (Treatment A; reference).

a For  $T_{max}$ , the median (minimum, maximum) is presented.

b Ratio of arithmetic means.

c The Wilcoxon signed-rank test was performed to calculate the p-value.

Treatment A = a single oral dose of Namenda XR 28-mg capsule and Aricept 10-mg tablet co-administered under fasted conditions.  
 Treatment B = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28-mg/10-mg capsule administered under fasted conditions.

$AUC_{0-t}$  = area under the plasma concentration versus time curve from time 0 to time t;  $AUC_{0-\infty}$  = area under the plasma concentration versus time curve from time 0 to infinity;  $C_{max}$  = maximum plasma drug concentration; CI = confidence interval; ER = extended release; LS = least squares;  $T_{1/2}$  = terminal elimination half-life;  $T_{max}$  = time of maximum plasma drug concentration; XR = extended release.

#### 6.3.1.4 Sponsor's Conclusions

The sponsor has concluded that the results of this study demonstrated the bioequivalence of both memantine and donepezil whether administered as a 28 mg capsule of Namenda® XR with a 10 mg tablet of donepezil or as the fixed-dose combination 28 mg/10 mg capsule.

The sponsor has also concluded that the no clinically significant safety signals were observed during the study, and that a single oral dose of MDX-8704 (28 mg/10 mg) was generally safe and tolerable.

#### 6.3.1.5 Reviewer's Comment

I concur with the sponsor's conclusion regarding the safety and tolerability of MDX-8704 in this study.

### 6.3.2 Study MDX-PK-105

#### 6.3.2.1 Outline Of Study Design

This was a randomized, open-label, single-dose, three-way cross-over study intended to evaluate the effect of food and the effect of sprinkling the capsule contents on applesauce on the relative bioavailability of memantine and donepezil after the oral administration of MDX-8704 (using the 28 mg/10 mg capsule strength).

The study was conducted in 36 healthy men and women, aged 18 to 45 years.

Subjects were assigned to one of 6 treatment sequences, in which each subject received Treatments A, B, and C (with a 21-day washout period between treatments), as depicted in the following table.

	<i>Period 1</i>	<i>Period 2</i>	<i>Period 3</i>
Sequence 1	Treatment A	Treatment B	Treatment C
Sequence 2	Treatment A	Treatment C	Treatment B
Sequence 3	Treatment B	Treatment A	Treatment C
Sequence 4	Treatment B	Treatment C	Treatment A
Sequence 5	Treatment C	Treatment A	Treatment B
Sequence 6	Treatment C	Treatment B	Treatment A

Treatments A, B, and C are explained below.

Treatment A: A single oral dose of the MDX-8704 28 mg/10 mg capsule administered under fasted conditions.

Treatment B: A single oral dose of the MDX-8704 28 mg/10 mg capsule administered after a high-fat meal.

Treatment B: A single oral dose of the MDX-8704 28 mg/10 mg capsule administered as capsule contents sprinkled on 30 mL (2 tablespoons) of apple sauce under fasted conditions.

#### 6.3.2.2 *Safety Results*

There were no deaths during the study. A single serious adverse event occurred in this study: a 25-year-old subject was detected to have an ectopic pregnancy after having a positive pregnancy test on Day 54, after completing all parts of the study. A 26-year old woman was discontinued from the study after ventricular extrasystoles were detected prior to dosing on Day 1 of Period 3; in Periods 1 and 2, she had received Treatments A and C, respectively; she also appears to have received Treatment B in Period C despite the detection of ventricular extrasystoles.

The incidence of treatment-emergent adverse events that occurred in 3 or more subjects overall is in the following table, which I have copied from the submission.

<i>System Organ Class Preferred Term</i>	<i>Treatment A (N = 35) n (%)</i>	<i>Treatment B (N = 34) n (%)</i>	<i>Treatment C (N = 34) n (%)</i>	<i>All Subjects<sup>a</sup> (N = 36) n (%)</i>
<b>At least 1 TEAE</b>	<b>22 (62.86)</b>	<b>15 (44.12)</b>	<b>23 (67.65)</b>	<b>29 (80.56)</b>
<b>Gastrointestinal system disorders</b>	<b>21 (60.00)</b>	<b>12 (35.29)</b>	<b>21 (61.76)</b>	<b>27 (75.00)</b>
Abdominal discomfort	3 (8.57)	2 (5.88)	2 (5.88)	5 (13.89)
Abdominal pain	0	1 (2.94)	2 (5.88)	3 (8.33)
Diarrhoea	0	0	3 (8.82)	3 (8.33)
Dyspepsia	1 (2.86)	1 (2.94)	1 (2.94)	3 (8.33)
Nausea	20 (57.14)	12 (35.29)	19 (55.88)	25 (69.44)
Vomiting	10 (28.57)	2 (5.88)	8 (23.53)	12 (33.33)
<b>General disorders and administration site conditions</b>	<b>3 (8.57)</b>	<b>0</b>	<b>3 (8.82)</b>	<b>6 (16.67)</b>
Feeling hot	1 (2.86)	0	2 (5.88)	3 (8.33)
<b>Nervous system disorders</b>	<b>17 (48.57)</b>	<b>7 (20.59)</b>	<b>15 (44.12)</b>	<b>21 (58.33)</b>
Dizziness	15 (42.86)	4 (11.76)	9 (26.47)	18 (50.00)
Headache	4 (11.43)	3 (8.82)	6 (17.65)	10 (27.78)

Notes: Medical Dictionary for Regulatory Activities Version 16.0 was used to code adverse events. Subjects were counted only once in each event category. A TEAE was assigned to the previous treatment if it occurred during a washout period. N = number of subjects in the Safety Population. n = number of subjects in the specific category. Percentages were calculated as  $100 \times (n/N)$ .

a Subjects who took any investigational product (counted only once).

Treatment A = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg capsule administered under fasted conditions.

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.

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.

ER = extended release; TEAE = treatment-emergent adverse event.

Note that study drug was administered without titration to all subjects participating in the study. Ordinarily (i.e., as recommended in the Prescribing Information), Namenda XR<sup>®</sup> would have been administered in a dose of 28 mg once daily only after titration over a period of 3 weeks, and donepezil would have been administered in a dose of 10 mg once daily only after titration over a minimum of 4 weeks.

Vital signs, electrocardiograms, safety laboratory tests, physical examinations, and suicidality assessments (the Columbia-Suicide Severity Rating Scale) were unremarkable for any data of concern besides those already described above.

### 6.3.2.3 Pharmacokinetic Results

The pharmacokinetic parameters and statistical analysis results for memantine are summarized in the following table, which I have copied from the submission. The table is self-explanatory.

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

Notes: A linear mixed effects model was fitted with sequence, treatment, and period as fixed effects and subjects within sequence as a random effect.

a For  $AUC_{0-\infty}$ , n = 22 for comparison between Treatments A and B and n = 20 between Treatments A and C because reliable  $AUC_{0-\infty}$  value could not be calculated for Subject 001-0016.

b For  $T_{max}$ , 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  $T_{max}$ .

d For  $T_{1/2}$ , 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.

Treatment A = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg capsule administered under fasted conditions.

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.

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.

$AUC_{0-t}$  = area under the plasma concentration versus time curve from time 0 to time t;  $AUC_{0-\infty}$  = area under the plasma concentration versus time curve from time 0 to infinity;  $C_{max}$  = maximum plasma drug concentration; CI = confidence interval; ER = extended release; LS = least squares;  $T_{max}$  = time of maximum plasma drug concentration;  $T_{1/2}$  = terminal elimination half-life.

The pharmacokinetic parameters and statistical analysis results for donepezil are summarized in the next table, which I have also copied from the submission.

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

Notes: A linear mixed effects model was fitted with sequence, treatment, and period as fixed effects and subjects within sequence as a random effect.

a For  $T_{max}$ , 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  $T_{max}$ .

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.

Treatment A = a single oral dose of MDX-8704 (memantine HCl ER/donepezil HCl) 28 mg/10 mg capsule administered under fasted conditions.

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.

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.

$AUC_{0-t}$  = area under the plasma concentration versus time curve from time 0 to time t;  $AUC_{0-\infty}$  = area under the plasma concentration versus time curve from time 0 to infinity;  $C_{max}$  = maximum plasma drug concentration; CI = confidence interval; ER = extended release; LS = least squares;  $T_{max}$  = time of maximum plasma drug concentration;  $T_{1/2}$  = terminal elimination half-life.

#### 6.3.2.4 Sponsor's Conclusions

The sponsor has concluded from the results of this study that food had no clinically meaningful effect on the bioavailability of the MDX-8704 capsule. The capsule was bioequivalent whether administered as an intact capsule or as capsule contents sprinkled in apple sauce.

The sponsor has also concluded that the incidence of treatment-emergent adverse events was similar for MDX-8704 (administered under fasted conditions) regardless of whether that formulation was administered as an intact capsule or as capsule contents sprinkled in apple sauce. Adverse events were generally lower when MDX-8704 (the 28 mg/10 mg capsule strength) was administered after a high-meal than in the fasted state. A single dose of MDX-8704 (28 mg/10 mg) was generally safe and well-tolerated in this study.

#### 6.3.2.5 Reviewer's Comment

I concur with the sponsor's conclusion regarding the safety and tolerability of MDX-8704 in this study.

## 7. Summary Of Clinical Pharmacology

In Section 2.5 of the submission, the sponsor has provided the following summary information.

The pharmacokinetics of memantine and donepezil have each been summarized using the text of the current approved Prescribing Information for Aricept<sup>®</sup> and Namenda XR<sup>®</sup>. Please see the text of the clinical pharmacology review of this application for further details. In addition:

- Study MEM-PK-07 did not demonstrate a significant pharmacokinetic or pharmacodynamic interaction between memantine and donepezil (the pharmacodynamic interaction was assessed using red blood cell acetylcholinesterase inhibition).
- Study MDX-PK-104 demonstrated bioequivalence between the to-be-marketed formulation of MDX-8704 and Namenda<sup>®</sup> XR administered together with donepezil as separate formulations.
- Study MDX-PK-105 demonstrated the lack of a food effect on exposure to donepezil and memantine when administered as MDX-8704.

## 8. Summary Of Biopharmaceutics

In Section 2.5 of the submission, the sponsor has drawn attention to the following items, among others:

- The dissolution profiles of the two strengths of MDX-8704 were similar as assessed by f2 values and was independent of pH at both strengths.
- *In vitro* dissolution studies did reveal alcohol dose dumping at 40% volume/volume alcohol; the sponsor believes that observation does not pose a serious safety concern.
- A Level A *in vitro in vivo* correlation was earlier established for the extended-release memantine (b)(4) formulation and submitted to NDA 22525 to secure the approval of lower strengths of Namenda XR<sup>®</sup>.

## 9. Summary Of Reviews By Other Agency Disciplines

A number of other disciplines within the Agency conducted reviews of this application.

The key conclusions of each of those reviews is summarized below. Please see the full text of those reviews for further details.

### **9.1 Pharmacology-Toxicology Review**

The Pharmacology-Toxicology review of this submission was conducted by Dr David Hawver of this Division, with a supervisory memorandum completed by Dr Lois Freed. Dr Hawver's review was completed on October 25, 2014, and Dr Freed's supervisory memorandum on November 23, 2014

Dr Hawver reviewed the results of the following 5 nonclinical studies, included in this application, and has summarized those results .

- Two neurotoxicity studies of the combination of donepezil and memantine that were conducted in rats. These were reviewed previously and are already described in the product labeling for memantine and donepezil products.
- An acute dose-ranging toxicity study of the combination of donepezil and memantine that was conducted in rats.
- Two studies of the possible cognitive efficacy of the combination of donepezil and memantine: one study was conducted in rats and the other in transgenic mice.

Dr Hawver considers this application approvable, also recommending changes to several sections of the Prescribing Information submitted by the sponsor. Dr Freed has concurred with Dr Hawver's recommendations.

### **9.2 Clinical Pharmacology Review**

The Clinical Pharmacology review of this application was conducted by Dr Xinning Yang.

His main conclusions may be summarized as follows.

- There was no significant effect of food on the bioavailability of memantine and donepezil administered as MDX-8704.
- The administration of MDX-8704 with the capsule contents sprinkled on applesauce was bioequivalent to the administration of the intact capsule (with both administered under fasted conditions).
- The median  $T_{max}$  of memantine was reduced to 14 hours from 24 hours when MDX-8704 was administered with food, consistent with the labeling for Namenda XR<sup>®</sup>.
- The median  $T_{max}$  of donepezil was prolonged to 6 hours when MDX-8704 was administered with a high-fat meal when compared with 3 hours when it was administered fasted conditions.

His main conclusions were based on his review of Study MDX-P-105. The pharmacokinetic data for Study MDX-P-104 were primarily reviewed by the Agency's Biopharmaceutics staff (see below).

Dr Yang considers this application acceptable from a Clinical Pharmacology standpoint, and has also recommended changes to several sections of the Prescribing Information submitted by the sponsor.

### **9.3 Chemistry, Manufacturing, And Controls Review**

The Chemistry, Manufacturing, and Controls aspects of this application were reviewed by Dr Pei-I Chu.

Dr Chu has conducted a detailed drug substance and drug product review of MDX-8704. She has noted that MDX-8704 is a capsule combination product containing two approved active ingredients (memantine and donepezil). She has further noted that the Office of Compliance has determined that the drug substance, drug product, and packaging facilities are acceptable, based on their profile.

Dr Chu has not reviewed the dissolution specifications for MDX-8704. She states that the Chemistry, Manufacturing, and Controls approval of this application would be contingent on an acceptable recommendation regarding the sponsor's dissolution specifications from the Biopharmaceutics reviewer.

The Chemistry review team has recommended changes to several sections of the text of the Prescribing Information submitted by the sponsor.

### **9.4 Biopharmaceutics Review**

The Biopharmaceutics review of this submission was performed by Dr Okpo Eradiri of the Office of New Drug Quality Assessment.

Dr Eradiri's review covered the following areas:

- The adequacy of the dissolution method and acceptance criteria for both components of the fixed-dose combination product.
- The results of the *in vitro* alcohol dose dumping study.
- The adequacy of the design, conduct, and results of the definitive bioequivalence study (MEM-PK-104) using the highest MDX-8704 dosage strength (28 mg/10 mg) proposed by the sponsor.
- The validity of the *in vivo in vitro* correlation method for the extended-release component of the product.
- The acceptability of the biowaiver request for the lower dosage strength (14 mg/10 mg) proposed by the sponsor.
- The acceptability of the biowaiver request for a manufacturing site change.

His main review of this submission was completed on October 26, 2014 at which time there was insufficient data available for the Biopharmaceutics staff to make a recommendation regarding the approvability of this application: the items pending at that time were the dissolution acceptance criteria for the drug product and the report of the inspection of an analytic site for Study MDX-PK-104. (The pending items were later made available to Dr Eradiri). Among the conclusions that he reached at his initial review was that the memantine and donepezil components of the 28 mg/10 mg capsule of MDX-8704 had been demonstrated to be bioequivalent to their respective single-entity reference products, based on his review of the pharmacokinetic data for MDX-PK-104.

In an addendum to his final review which was completed on November 21, 2014, Dr Eradiri reviewed the data that were pending at the time he completed his initial review on October 26, 2014. In his final conclusion, he found that the data submitted with this application were acceptable and recommended approval of the application.

Dr Eradiri has not recommended any changes to the text of the submitted Prescribing Information for this product.

### **9.5 Proprietary Name Review**

The sponsor proposed the proprietary name "NAMZARIC" for the fixed-dose combination product whose approval had been sought under this application.

A review of the proprietary name "NAMZARIC" was conducted by Justine Harris, RPh, of the Division of Medical Error Prevention and Analysis of the Office of Surveillance and Epidemiology. She concluded that the proprietary name "NAMZARIC" was acceptable from a promotional, as well as safety, perspective. The grant of that proprietary name was later confirmed in a letter to the sponsor from the Office of Medical Error Prevention and Risk Management, dated May 23, 2014.

Ms Harris also conducted a labeling review for this application which was completed on September 30, 2014. She made a number of recommendations regarding the Prescribing Information, Patient Package Insert (Patient Prescribing Information), and container labels. Her recommended changes to the Prescribing Information were given due consideration when the Prescribing Information was finalized.

## **10. Site Inspection Report**

An analytical site inspection was conducted for Study MEM-PK-104 by the Division of Bioequivalence and Good Laboratory Practices Compliance (of the Office of Scientific Investigations) at the request of this Division. That inspection was conducted between August 11 and 15, 2014, at Forest Research Institute, Inc., Farmingdale, NY. At the conclusion of that inspection, Form FDA 483 was

issued by the Agency. The sponsor responded on September 8, 2014 to the deficiencies earlier noted by the Agency in the Form FDA 483 issued at the conclusion of the inspection. The Division of Bioequivalence and Good Laboratory Practices Compliance concluded based on the inspection itself and the sponsor's responses dated September 8, 2014, that the analytical data for Study MEM-PK-104 were reliable.

A clinical site inspection was also requested by this Division for Study MEM-PK-104. That request was declined by the Division of Bioequivalence and Good Laboratory Practices Compliance (of the Office of Scientific Investigations) as the site in question ((PPD Phase 1 Clinic, Austin, TX) had been inspected four times over the past 2 years (in connection with other New Drug Applications): those inspections were performed during and after the conduct of Study MEM-PK-104 did not reveal any adverse items; and those inspections in themselves provided assurance that Study MDX-P-104 was conducted without significant irregularities.

## 11. Labeling

The Prescribing Information provided by the sponsor is (as was confirmed by this reviewer) in large measure a combination of the approved Prescribing Information for Namenda XR<sup>®</sup> and the elements of the approved Prescribing Information for Aricept<sup>®</sup> that are pertinent to the 10 mg tablet strength and to the indication being sought under the current application.

The contents of the Prescribing Information were first reviewed by Agency staff other than this reviewer and editorial changes made. This reviewer included a description of clinical trials conducted with donepezil in severe Alzheimer's Disease (these data were copied from the labeling for Aricept<sup>®</sup>). Beyond that, this reviewer's role was that of making minor editorial changes to the labeling and in confirming (in conjunction with other staff within this Division) that the labeling was consistent with the Physicians Labeling Rule.

The draft Prescribing Information finalized by this reviewer is in a separate document.

The Patient Prescribing Information (Patient Package Insert) for this submission has also been reviewed by me.

Please also note the following.

As already stated above, the Division of Medical Error Prevention and Analysis of the Office of Surveillance and Epidemiology has reviewed Prescribing Information, Patient Package Insert (Patient Prescribing Information), and container labels. In addition:

- The Division of Medical Policy Programs of the Office of Medical Policy has reviewed the Patient Package Insert (Patient Prescribing Information).

- The Office of Prescription Drug Promotion has reviewed the Prescribing Information, and Patient Package Insert (Patient Prescribing Information).

The labeling recommendations of all the above staff were also duly considered when finalizing the label for MDX-8704 (NAMZARIC).

## **12. Financial Disclosure Certification**

Financial disclosure information (in accordance with 21 CFR Part 54) has been provided for two clinical studies that have already been described in more detail earlier in this review.

- MDX-PK-104.
- MDX-PK-105.

### **12.1 Components Of Certification**

#### **12.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests (FDA Form 3454)**

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in these studies. In regard to this list the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

### **12.2 Reviewer's Comment**

It appears unlikely that the financial information disclosed in this application introduced significant bias into results of Studies MDX-PK-104 and MDX-PK-105.

### **13. Pediatric Waiver Request**

In this application, the sponsor has submitted a request for a full waiver of the requirement (under the Pediatric Research Equity Act) to conduct studies of MDX-8704 in children aged 0 to 17 years.

The basis for that request is that Alzheimer's Disease occurs only in adults: pediatric studies of MDX-8704 will therefore be impossible or highly impractical.

The sponsor has further certified the basis for seeking a waiver from the requirement to conduct pediatric studies of MDX-8704.

The initial Pediatric Study Plan for MDX-8704 was submitted to IND 109763 (Serial Number 019) on November 15, 2013; that submission included a statement that the sponsor intended to seek a pediatric waiver for that product. At a meeting of the Agency's Pediatric Review Committee (PeRC) Best Pharmaceuticals for Children Act (BPCA)/Pediatric Study Plan Subcommittee held on January 15, 2014, it was agreed that MDX-8704 qualified for a full waiver of the requirement to conduct pediatric studies.

#### **13.1 Reviewer's Comment**

A full waiver of the requirement (under the Pediatric Research Equity Act) to conduct studies of MDX-8704 in children aged 0 to 17 years may be granted.

### **14. Overall Conclusion**

This New Drug Application provides substantial evidence for the efficacy and safety of MDX-8704 (NAMZARIC), a fixed-dose combination drug product (capsule) consisting of extended-release memantine hydrochloride and donepezil hydrochloride for the treatment of moderate to severe dementia of the Alzheimer's type.

### **15. Recommendation**

I recommend that MDX-8704 (NAMZARIC), a fixed-dose combination drug product (capsule) consisting of extended-release memantine hydrochloride and donepezil hydrochloride, be approved for the treatment of moderate to severe dementia of the Alzheimer's type.

No post-marketing commitments by the sponsor are necessary.

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Ranjit B. Mani, M.D.  
Medical Reviewer

rbm

cc:

HFD-120

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/s/  
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RANJIT B MANI  
12/19/2014

### Review and Evaluation of Clinical Data

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NDA	206439
Sponsor:	Forest
Drug:	MDX-8704
Proposed Indication:	Alzheimer's Disease
Material Submitted:	New Drug Application/Labeling
Correspondence Date:	2/26/14
Date Received / Agency:	2/26/14
Date Review Completed:	12/19/14
Reviewer:	Ranjit B. Mani, M.D.

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#### Background

This New Drug Application (NDA) seeks the approval of two strengths of MDX-8704, a fixed-dose combination drug product (capsule) containing extended-release memantine hydrochloride and donepezil hydrochloride as components, for the treatment of moderate to severe dementia of the Alzheimer's type (i.e., Alzheimer's Disease).

The contents of this file are intended to accompany the main review of this application. They comprise a draft version of the Prescribing Information and Patient Package Insert for MDX-8704 (NAMZARIC). This version was finalized after receiving input from all other review disciplines with this Agency and from supervisory staff within this Division. Please note that the draft Prescribing Information and Patient Package Insert in this document may not be identical to the Prescribing Information and Package that may accompany the action letter for this application.

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Ranjit B. Mani, M.D.  
Medical Reviewer

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RANJIT B MANI  
12/19/2014