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APPLICATION NUMBER:

206439Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	**206439**
Sponsor:	**Forest**
Drug:	**MDX-8704**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
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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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.

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