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APPLICATION NUMBER:

206439Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206439
Applicant Name	Forest Laboratories
Date of Submission	2/26/14
PDUFA Goal Date	12/26/14
Proprietary Name/ **Established (USAN) Name**	Namzaric/extended-release memantine hydrochloride and donepezil hydrochloride
Dosage Forms/Strength	Oral capsule/extended-release memantine combined with donepezil in once daily doses of 28 mg/10 mg or 14 mg/10 mg
Proposed Indication(s)	Treatment of moderate to severe dementia of the Alzheimer's type
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ranjit Mani, MD
Statistical Review	Xiaoyu Dong, PhD
Pharmacology Toxicology Review	David Hawver, PhD
CMC/OBP Review	Pei-I Chu, PhD; Okpo Eradiri, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Xinning Yang, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	Gajendiran Mahadevan, PhD
CDTL Review	Ranjit Mani, MD
OSE/DMEPA	Justine Harris, RPh
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Sharon Williams, MSN, BSN, RN
PMHS	N/A
SEALD	N/A
Other	N/A

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

This submission is an application for the approval of a fixed-dose combination (which, for convenience, I will call MDX in this memo, drawn from its investigational designation of MDX-8704) of extended-release memantine (MEM) and donepezil (DPZ) in doses of MEM 28 mg combined with DPZ 10 mg (28/10) and MEM 14 mg combined with DPZ 10 mg (14/10).

Extended-release memantine is an approved drug for the treatment of moderate to severe dementia of the Alzheimer's type, marketed by the sponsor of the current application as Namenda XR in various strengths, including 14 mg and 28 mg. Donepezil is an approved drug for the treatment of mild, moderate, and severe dementia of the Alzheimer's type, marketed as Aricept in various strengths, including 10 mg.

This application is supported by cross-reference to the sponsor's own approved memantine (Namenda) and extended-release memantine (Namenda XR) applications, reliance on our previous finding of safety and effectiveness for approved donepezil (Aricept), clinical pharmacology studies intended to evaluate bioequivalence and bioavailability of the new product, additional nonclinical studies, and manufacturing information.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

This is the first application for this product. The underlying rationale for this product is that of a combination of convenience, as Namenda XR and donepezil are frequently taken together in clinical use, and such a combination should simplify administration and enhance compliance with prescribed therapy. During development, the sponsor discussed the rationale for the development of MDX with us and reached agreement with us on the proposed basis for approval described above over the course of several meetings, including an end of Phase 2 meeting on October 13, 2011, a Type C meeting on June 20, 2013, and a pre-NDA meeting on November 19, 2013. There are no outstanding issues from those meetings.

3. CMC/Device

I concur with the conclusions reached by Dr. Chu, Dr. Eradiri, and Dr. Dong regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The sponsor submitted additional nonclinical studies of the combination of MEM and DPZ. In addition to evaluating toxicity and dose-ranging, the submitted studies included data the sponsor argues support a synergistic effect of MEM and DPZ on cognitive function and acetylcholine levels. Dr. Hawver reviewed these data, as did the nonclinical supervisor, Dr. Lois Freed, and both Dr. Hawver and Dr. Freed find that the data are insufficient to support such a synergistic effect due to lack of concurrent controls, small numbers of animals per group, and the absence of individual animal data to allow independent analyses. I concur with the conclusions reached by Dr. Hawver that there are no outstanding nonclinical issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted additional clinical pharmacology studies intended to establish the bioequivalence of MDX with the combination of individually administered Namenda XR and donepezil and assess the characteristics of the combination. Dr. Eradiri reviewed these data and found that high dose MDX (28/10) was bioequivalent to its co-administered individual components. Dr. Eradiri reviewed the request for a biowaiver for low dose MDX (14/10) and found it acceptable. Dr. Yang reviewed the food effect study and found no clinically significant effect of food on the bioavailability of MDX. I concur with the conclusions reached by Dr. Eradiri and Dr. Yang that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Efficacy is addressed by assessment of bioequivalence to drugs of known effectiveness. There are no new efficacy data. I note that each component of MDX has a different presumed mechanism of action in Alzheimer's dementia. I also note that the primary study supporting approval of Namenda XR was of an add-on design, superimposing Namenda XR on a background of stable acetylcholinesterase inhibitor therapy, about 70% of which was donepezil.

8. Safety

Safety parameters in the clinical pharmacology studies were reviewed in detail by Dr. Mani and are presented in his memo containing both his primary review findings and his recommendations as Cross-Discipline Team Leader. The safety profile of MDX, as assessed in the clinical pharmacology studies, is consistent with the know safety profiles of its individual components, and Dr. Mani finds no safety issues of concern. I concur with the conclusions reached by Dr. Mani that there are no outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

We are waiving the pediatric study requirement for this application because dementia of the Alzheimer's type does not occur in children.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The sponsor has provided substantial evidence of effectiveness for MDX based on cross-reference to the sponsor's own approved memantine (Namenda) and extended-release memantine (Namenda XR) applications, reliance on our previous finding of safety and effectiveness for approved donepezil (Aricept), and a demonstration of bioequivalence of MDX to its co-administered individual components (Namenda XR and donepezil). The independent contribution of each component of this fixed-dose combination has been established by these findings. Further, this combination should result in increased

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