CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022568

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: July 8, 2010

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-568 (SDN 1 [September 24, 2009], SDN 11 [June 3, 2010]), Aricept 23 mg Tablets, Eisai Medical Research

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The sponsor has submitted an NDA for a new dosage strength (23 mg) of Aricept (donepezil hydrochloride). Aricept is currently marketed as immediate-release and orally-disintegrating tablets (5 and 10 mg) for treatment of mild-to-moderate, as well as severe Alzheimer's disease. While the sponsor characterizes the new formulation as an extended-release tablet, the ONDQA Biopharmaceutics Lead has concluded that the sponsor did not provide "…the necessary studies required…to establish the controlled release nature of the formulation…" (Biopharmaceutics Review NDA #22568, Patrick Marroum, Ph.D., 4/2/2010).

No nonclinical studies were submitted in the NDA; however, the higher dose provided by this product necessitates recalculation of safety margins for product labeling. Also, labeling is being revised to PLR format. Dr. Hawver has addressed the labeling issues in his review (Pharmacology/Toxicology NDA Review and Evaluation NDA 22-568, 7/2/2010). Dr. Hawver has also addressed concerns raised since Aricept was originally approved regarding the use of Aricept in combination with another approved Alzheimer's disease therapy (memantine).

In 2008, Creeley *et al*. (Creeley CE *et al*. *Neurobiol Aging* 29(2):153-167, 2008) reported an increase in neurotoxicity (widespread neurodegeneration) when donepezil was administered in combination with memantine to rats, with both drugs being given by intraperitoneal injection. Although Creeley *et al*. (2008) did not use the clinical route of administration, the clinical relevance of the findings cannot be dismissed. Both drugs are commonly used in combination in Alzheimer's patients due, in part, to their different mechanisms of action.

I concur with Dr. Hawver's recommendation for an acute oral neurotoxicity study of the combination as a postmarketing requirement (PMR). This study will further investigate

the Creeley *et al*. (2008) findings using the clinical route of administration. Language for the PMR has been provided in a separate document (*Aricept PMR/PMC Development Template*).

Dr. Hawver does not recommend including a description of the Creeley *et al*. (2008) results in the Aricept labeling, but it is my opinion that it should be, particularly considering the higher clinical dose provided by this new dosage strength (23 vs 10 mg). In addition, the Creeley *et al*. (2008) findings have been added to the most recent version of labeling for Namenda (memantine).

Recommended Labeling: the following labeling recommendations are made taking into account Dr. Hawver's proposed labeling, but are also based on examination of study results as reviewed by Dr. Rosloff (Pharmacologist Review of NDA 20-690 Original summary, 6/6/96; NDA 20-690 - Submission of 1/30/03, 4/17/03).

Regarding the Mutagenesis section of labeling, it is recommended that (b) (4)

The basis for recommending the addition of Section 13.2 wording is discussed above.

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------USE IN SPECIFIC POPULATIONS--------

- Based on animal data, may cause fetal harm (8.1)

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies in pregnant women. ARICEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of donepezil to pregnant rats and rabbits during the period of organogenesis did not produce any teratogenic effects at doses up to 16 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m^2 basis) and 10 mg/kg/day (approximately 7 times the MRHD), respectively. Oral administration of donepezil (1, 3, 10 mg/kg/day) to rats during late gestation and throughout lactation to weaning produced an increase in stillbirths and reduced offspring survival through postpartum day 4 at the highest dose. The no-effect dose of 3 mg/kg/day is approximately equal to the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

It is not known whether donepezil is excreted in human milk. Caution should be exercised when Aricept is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Aricept in children have not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil (b) (4)

(b) (4)

Donepezil had no effect on fertility in rats at oral doses up to 10 mg/kg/day (b) (4)

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

LOIS M FREED
07/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22-568
Supporting document/s:	1, 11
Applicant's letter date:	September 24, 2009, June 3, 2010
CDER stamp date:	September 24, 2009, June 3, 2010
Product:	Aricept 23 mg Tablets (donepezil hydrochloride)
Indication:	Treatment of moderate to severe dementia of the Alzheimer's type
Applicant:	Eisai Medical Research, Woodcliff Lake, NJ
Review Division:	Division of Neurology Products
Reviewer:	David B. Hawver, Ph.D.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell Katz, M.D.
Project Manager:	Teresa A. Wheelous

Disclaimer

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APPENDIX 1: 7
NONCLINICAL SECTIONS OF THE LABELING PROPOSED BY THE SPONSOR, WITH REVIEWER'S RECOMMENDED REVISIONS PRESENTED IN RED 7

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a Pharmacology/Toxicology perspective, this application is approvable.

1.1.2 Additional Nonclinical Recommendations

Aricept is often used clinically in combination with Namenda (memantine HCl). Based on the finding that donepezil can potentiate the neurodegeneration induced by memantine in rat brain (Creeley et al. *Neurobiology of Aging* 29: 153-167, 2008), the Sponsor should conduct a single dose oral neurotoxicity study in female rats (at least 10 per group) with donepezil and memantine, each administered alone and in combination. Doses of donepezil and memantine should range from those estimated to result in plasma exposures similar to those observed at the maximum recommended clinical doses (i.e., 23 mg/day donepezil and 28 mg/day memantine), up to maximum tolerated doses. Two positive control groups should be included, one treated with 30 mg/kg i.p. memantine + 10 mg/kg i.p. donepezil (for comparison to the results of Creeley et al., 2008) and one treated with 3 mg/kg i.p. MK-801. Neurohistopathology should be assessed at 48 hrs after dosing using standard cupric silver staining methods, and should include examination of all brain regions shown to be affected by Creeley et al. (2008). Toxicokinetic analyses of donepezil and memantine should be performed for the oral and i.p. treated groups. This study should be conducted as a Post-marketing Requirement.

1.1.3 Labeling

The proposed labeling should be revised to PLR format and to reflect the lowered safety margins for the reproductive and developmental toxicity studies (Section 8.1.) and the carcinogenicity and fertility studies (Section 13.1.) since the maximum recommended human dose is being increased from 10 mg to 23 mg. See Appendix 1 for detailed recommendations.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were included in this submission.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

120011-70-3

2.1.2 Generic Name

Donepezil hydrochloride

2.1.3 Code Name

E 2020

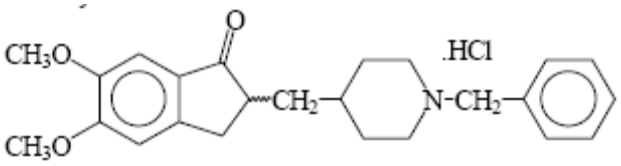
2.1.4 Chemical Name

(±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride

2.1.5 Molecular Formula/Molecular Weight

Molecular formula/molecular weight: $C_{24}H_{29}NO_3 \bullet HCl$ / 415.95

2.1.6 Structure



2.1.7 Pharmacologic class

Acetylcholinesterase inhibitor

2.2 Relevant INDs, NDAs, and DMFs

NDA 20-690 Donepezil HCl (5 and 10 mg oral tablets) approved 25 NOV 1996 for the treatment of mild to moderate dementia of the Alzheimer's type, and 13 OCT 2006 for the treatment of severe dementia of the Alzheimer's type, Eisai Inc.

NDA 21-719 Donepezil HCl (5 and 10 mg oral solutions) approved 18 OCT 2004 for the treatment of mild to moderate dementia of the Alzheimer's type, Eisai Inc.

NDA 21-720 Donepezil HCl (5 and 10 mg orally disintegrating tablets) approved 18 OCT 2004 for the treatment of mild to moderate dementia of the Alzheimer's type, and 13 OCT 2006 for the treatment of severe dementia of the Alzheimer's type, Eisai Inc.

IND 35,974 Donepezil HCl tablets for the treatment of mild to moderate dementia of the Alzheimer's type, Eisai Inc.

2.3 Clinical Formulation

2.3.1 Drug Formulation

Each film-coated tablet contains 23 mg donepezil HCl along with the following inactive ingredients: lactose monohydrate, ethylcellulose, methacrylic acid copolymer (Type C), hydroxypropyl cellulose, magnesium stearate, and (b) (4)

2.3.2 Comments on Novel Excipients

There are no novel excipients in the clinical formulation.

2.3.3 Comments on Impurities/Degradants of Concern

No concerns.

2.4 Proposed Clinical Population and Dosing Regimen

Aricept 23 mg is indicated for the treatment of moderate and severe dementia of the Alzheimer's type. The recommended starting dosage is Aricept 5 mg once daily. Dose escalations to the next higher dose (i.e., 5 mg → 10 mg → 15 mg → 20 mg → 23 mg) should not occur until the patient has been established on the previous dose for at least 4 to 6 weeks. The maximum recommended dose is 23 mg once daily.

2.5 Regulatory Background

This is an original NDA submission for Aricept 23 mg oral tablets, an increased dosage strength of donepezil HCl, for the treatment of moderate and severe dementia of the Alzheimer's type. Lower dosage strengths of donepezil HCl (Aricept 5 and 10 mg) were approved in 1996 (tablet) and 2004 (oral solution and oral disintegrating tablets).

3 Studies Submitted

3.1 Studies Reviewed

None. (See Pharmacologist Reviews for NDA 20-690 listed in Section 3.3 below)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Pharmacologist Review of NDA 20-690 E 2020 (donepezil, Aricept®) for Alzheimer's disease, Barry N. Rosloff, Ph.D., 06 JUN 1996

Pharmacologist Review of NDA 20-690 (88-wk mouse and 104-wk rat oral carcinogenicity studies), Barry N. Rosloff, Ph.D., 24 JAN 2000

Pharmacologist Review of NDA 20-690 (Proposed changes to the Carcinogenesis and Mutagenesis sections of the Aricept labeling), Barry N. Rosloff, Ph.D., 16 APR 2003

12 Appendix/Attachments

APPENDIX 1:

Nonclinical Sections of the Labeling Proposed by the Sponsor, with Reviewer's Recommended Revisions Presented in Red

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. ARICEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(b) (4)

(b) (4) **Nursing Mothers**

It is not known whether donepezil is excreted in human (b) (4) milk. (b) (4)

(b) (4) **Pediatric Use**

(b) (4)

(b) (4) **Geriatric Use**

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. (b) (4) The efficacy and safety data presented in the clinical trials section were obtained from these patients.

There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old.

8.6. Lower Weight Individuals

In the controlled clinical trial, among patients in the ARICEPT 23 mg treatment group, those patients weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse events as well. This finding may be related to higher plasma exposure associated with lower weight (b) (4).

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (b) (4) or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (b) (4).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (b) (4).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

DAVID B HAWVER
07/02/2010

LOIS M FREED
07/07/2010
See memo for comments and labeling recommendations.