CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-720

Chemistry Review(s)
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720
CHEM.REVIEW #5
REVIEW DATE: 18-OCT-04

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<td>Amendment</td>
<td>04-OCT-04</td>
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NAME & ADDRESS OF APPLICANT:
Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) ODT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#: AChEsterase Inhibitor/2013060
Chem.Type/Ther.Class:

PHARMACOL.CATEGORY/INDICATION: AD

DOSAGE FORM: Tablets
STRENGTHS: 5 mg & 10 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_______OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (+)-2,3-dihydro-5,6-dimethoxy-2-[(1-(phenylmethyl)-4-piperidinyl)methyl]-1H-inden-1-one HCl
CAS name: (+)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C24H29NO3.HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0

SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)

RELATED DOCUMENTS: none

REMARKS/COMMENTS: The newly proposed full proprietary name Aricept ODT (donepezil hydrochloride orally disintegrating tablets) is unacceptable. The sponsor must change it to: Articept ODT (donepezil hydrochloride) orally disintegrating tablet. In addition, the OC withdrew the acceptable overall recommendation and is now waiting for the GMP inspection to take place in the future (Kashima/Kawashima problem).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 21-720 APPROVABLE, subject to the resolution of proprietary name issue and the completion of inspection.

cc:
Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by: MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.005.doc
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/s/

Janusz Rzeszotarski
10/18/04 09:03:46 AM
CHEMIST

Maryla Guzewska
10/18/04 09:12:17 AM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720

SUBMISSION TYPE: ORIGINAL
DOCUMENT DATE: 17-DEC-03
CDER DATE: 18-DEC-03
ASSIGNED DATE: 05-JAN-04

NAME & ADDRESS OF APPLICANT:
Eisai Medical Research Inc.
500 Frank W. Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
- Proprietary:
- Nonproprietary/USAN:
- Code Name/#: Donepezil hydrochloride
- Chem.Type/Ther.Class:

AChEsterase Inhibitor/2013060

PHARMACOL. CATEGORY/INDICATION: AD

DOSAGE FORM:
Tablets
STRENGTHS:
5 mg & 10 mg
ROUTE OF ADMINISTRATION:
Oral
DISPENSED:
XXXXX Rx____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
- IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl
- CAS name: (±)-2-[[1-benzyl-4-piperidyl]methyl]-5,6-dimethoxy-1-indanone hydrochloride
- Molecular formula: C24H29NO3.HCl
- Relative molecular mass: Mr = 415.95
- CAS Registry number: 142057-70-0

SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)

RELATED DOCUMENTS: none

REMARKS/COMMENTS: The Office of Compliance issued an overall recommendation of all facilities now being acceptable. (see the attached copy of EER). Therefore, the only still remaining issue is the unfortunate attempt to call Aricept Orally Disintegrating Tablets by the name ___.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 21-720 APPROVABLE, subject to the resolution of proprietary name issue.

cc:
Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by: MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.004.doc
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/s/

Janusz Rzeszotarski
9/27/04 12:10:44 PM
CHEMIST

Maryla Guzewska
9/28/04 08:13:00 AM
CHEMIST
**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

**Review of Chemistry, Manufacturing, and Controls**

**NDA #: 21-720**

**CHEM.REVIEW # 3**

**REVIEW DATE: 16-SEP-04**

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<td>03-SEP-04</td>
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**NAME & ADDRESS OF APPLICANT:**

Eisai Medical Research Inc.
500 Frank W.Burr Blvd
Teaneck, NJ 07666

**DRUG PRODUCT NAME**

- Proprietary: Aricept (donepezil hydrochloride) ODT
- Nonproprietary/USAN: Donepezil hydrochloride
- Code Name/#: AChEsterase Inhibitor/2013060

**PHARMACOL.CATEGORY/INDICATION:**

AD

**DOSAGE FORM:**

Tablets

**STRENGTHS:**

5 mg & 10 mg

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:**

XXXXX Rx _______ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

- **IUPAC name:** (±)-2,3-dihydro-5,6-dimethoxy-2-[(1-(phenylmethyl)-4-piperidinyl)methyl]-1H-inden-1-one HCl
- **CAS name:** (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
- **Molecular formula:** C24H29N03.HCl
- **Relative molecular mass:** Mr = 415.95
- **CAS Registry number:** 142057-77-0

**SUPPORTING DOCUMENTS:** NDA 20-690 (Aricept Tablets)

**RELATED DOCUMENTS:** none

**REMARKS/COMMENTS:** In the response to request to change the name from Aricept® Rapidly Disintegrating Tablets to Aricept® Orally Disintegrating Tablets the sponsor brings in a new name: [donepezil HCl] orally disintegrating tablets. This proposed, new, proprietary name has never been reviewed by the DMETS and is unacceptable. Therefore, both, the proposed drafts of commercial presentations and labeling are unacceptable. The sponsor was urged to combine the labeling for all three formulations. Instead a separate labeling for the [donepezil HCl] was submitted. The proprietary name must be either reviewed by DMETS or changed back to the proposed name: Aricept® (donepezil HCl) orally disintegrating tablets.

**CONCLUSIONS & RECOMMENDATIONS:** There is one facility still waiting for the EER recommendation as of 15-SEP-2004. Recommend NDA 21-720 APPROVABLE, subject to: OC EER recommendation and to resolution of the proprietary name issue.

cc:

Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MEGriffis
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.003.doc
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janusz Rzeszotarski
9/17/04 07:32:00 AM
CHEMIST

John Simmons
9/20/04 11:05:17 AM
CHEMIST
for M Guzewska
NDA 21-720

Aricept (donepezil HCl) Orally Disintegrating Tablets

Eisai Medical Research

Chemistry Review
W. Janusz Rzeszotarski, Ph.D.
HFD-120
Table of Contents

Table of Contents.................................................................................................................. 1
Chemistry Review Data Sheet................................................................................................. 2
The Chemistry Executive Summary......................................................................................... 5

I. Recommendations............................................................................................................. 5
   A. Recommendations and Conclusions on Approvability................................................. 5
   B. Recommendations on Phase IV (Post-Marketing) Commitments, Agreements,
      and/or Risk Management Steps, if Approvable......................................................... 5

II. Summary of Chemistry Assessments............................................................................. 5
    A. Description of the Drug Product and Drug Substance............................................. 5
    B. Description of How the Drug Product is Intended to be Used............................... 5
    C. Basis for Approvability or Not Approvability......................................................... 6

III. Administrative............................................................................................................... 6
Chemistry Assessment........................................................................................................... 7

Appears This Way
On Original
Chemistry Review Data Sheet

1. **NDA #** 21-720

2. **REVIEW #:** 2

3. **REVIEW DATE:** 12-JUL-2004

4. **REVIEWER:** W. Janusz Rzeszotarski, Ph.D.

5. **PREVIOUS DOCUMENTS:**

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6. **SUBMISSION(S) BEING REVIEWED:** An amended submission.

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<td>Amendment (BC)</td>
<td>11-AUG-04</td>
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7. **NAME & ADDRESS OF APPLICANT:**

   **Name:** Eisai Medical Research  
   **Address:** 500 Frank W. Burr Blvd  
                 Jersey City, NJ 07311  

   **Representative:** Charles J. Callagan  
   **Telephone:** 201-287-2242

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary: Aricept ODT  
   b) Non-Proprietary: Donepezil hydrochloride  
   c) Code Name/#  
   d) Chem. Type/Submission Priority: 3S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOL. CATEGORY:** Treatment of moderate to severe Alzheimer's Disease

11. **DOSAGE FORM:** Orally disintegrating tablet

12. **STRENGTH/POTENCY:** 5 mg & 10 mg

13. **ROUTE OF ADMINISTRATION:** Oral
14. Rx/OTC DISPENSED:  _X_ Rx  __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[1-(phenylmethyl)-4-piperidinylmethyl]-1H-inden-1-one
HCl
CAS name: (±)-2-[1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C24H29NO3.HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0

16. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A

B. Other Documents:

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18. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

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The Chemistry Executive Summary

I. **Recommendations**

A. **Recommendation and Conclusion on Approvability**

Aricept ODT (Orally Disintegrating Tablets) are tablets containing 5 or 10 mg of donepezil hydrochloride. The application refers to the approved NDA 20-690 for the information on donepezil hydrochloride drug substance. The manufacturer, the method of manufacture and the specifications for the drug substance have not been changed. The need for the orally disintegrating tablet designed for the AD patients is well justified (impaired salivation, coordination and swallowing). The tablet manufacturing technique is well established and proven for other similar drug products (Risperdal M-Tabs, Claritin RediTabs, Zebatin, etc.). The 5 mg and 10 mg investigational formulations used in the bioequivalence studies and the proposed commercial formulations are the same. Investigational formulations were produced at a batch size of \[ \mathcal{O} \] tablets. The commercial batch size is \[ \mathcal{O} \] tablets. \( \mathcal{O} \) commercial scale batches manufactured at the proposed Eisai Co. Ltd. commercial manufacturing (ECL-Misato) facility in Misato, Japan and \( \mathcal{O} \) pilot scale batches manufactured at the Eisai Co. Ltd. Formulation Research Laboratory in Kawashima, Japan met the proposed release specifications. Primary stability is provided for three lots each of the 5 mg and 10 mg donepezil hydrochloride orally disintegrating tablets in the container/closure system intended for marketing. The primary stability batches were manufactured at ECL-Misato at full scale using the commercial formulation and equipment and packaged at the Eisai Inc. (ESI-RTP) facility in Research Triangle Park, North Carolina, the proposed packaging site. Supportive stability data is provided including data on these and other batches packaged into container/closure configurations not selected for marketing. Potential degradation products of donepezil hydrochloride in the drug products will be monitored as follows: \[ \mathcal{O} \] The proposed limits are supported by available stability data on the new dosage form and are consistent with the limits for approved Aricept Tablets in NDA 20-690 and recommended ICH limits for identified and unidentified impurities in the ICH Guidelines for Impurities in New Drug Products (February 5, 2003).

The sponsor provided satisfactory data to prove the reproducibility of manufacturing process and the purity and stability of the drug product.

The Establishment Evaluation System still shows two of the listed facilities scheduled for inspection as of 25-AUG-2004. The RFI of 17-JUN-04 produced response on 11-AUG-04, which addresses the total levels of impurities/degradants in the drug product. Therefore, at present the application has to be recommended as APPROVABLE subject to establishment evaluation and establishment of proper (Orally instead Rapidly) name for the drug product.
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

Donepezil hydrochloride is an inhibitor of acetylcholine esterase that shows a decreased level of side effects. The rapidly disintegrating formulation will assist the patients with impaired swallowing ability (decreased salivation, impaired coordination and swallowing).

A. Description of the Drug Product and Drug Substance

Drug Product. The proposed commercial products are orally disintegrating tablets containing 5 or 10 mg of donepezil hydrochloride. The 5 mg dosage strength is a round, white tablet with a diameter of 9.5 mm and a tablet weight of 280 mg. The 10 mg dosage strength is a round, yellow tablet with a diameter of 9.5 mm and tablet weight of 280 mg. The tablets are differentiated by embossing and color. The manufacturing process involves \[ \text{consisting of donepezil hydrochloride, mannitol, carrageenan, colloidal silicon dioxide, and purified water.} \]

\[ \text{with mannitol (and yellow ferric oxide for the 10 mg dosage form). The granules} \]

\[ \text{polyvinyl alcohol solution,} \]

\[ \text{The 5 mg and 10 mg} \]

\[ \text{investigational formulations used in the bioequivalence studies and the proposed commercial} \]

\[ \text{formulations are the same. Investigational formulations were produced at a batch size of} \]

\[ \text{J} \]

\[ \text{J tablets.} \]

\[ \text{The commercial batch size is} \]

\[ \text{J tablets.} \]

\[ \text{J commercial scale batches manufactured at the} \]

\[ \text{proposed Eisai Co. Ltd. commercial manufacturing (ECL-Misato) facility in Misato, Japan and} \]

\[ \text{pilot scale batches manufactured at the Eisai Co. Ltd. Formulation Research Laboratory in Kawashima, Japan} \]

\[ \text{met the proposed release specifications. Primary stability is provided for three lots each of the 5 mg} \]

\[ \text{and 10 mg donepezil hydrochloride rapid disintegration tablets in the container/closure system} \]

\[ \text{intended for marketing.} \]

\[ \text{The primary stability batches were manufactured at ECL-Misato at full scale} \]

\[ \text{using the commercial formulation and equipment and packaged at the Eisai Inc. (ESI-RTP) facility in} \]

\[ \text{Research Triangle Park, North Carolina, the proposed packaging site. Supportive stability data is} \]

\[ \text{provided including data on these and other batches packaged into container/closure configurations not} \]

\[ \text{selected for marketing.} \]

\[ \text{Potential degradation products of donepezil hydrochloride in the drug products will be monitored as} \]

\[ \text{follows} \]

\[ \text{The proposed limits are supported by available stability data on the new dosage form and} \]

\[ \text{are consistent with the limits for approved Aricept Tablets in NDA 20-690 and recommended ICH limits for} \]

\[ \text{identified and unidentified impurities in the ICH Guidelines for Impurities in New Drug Products (February 5,2003).} \]

\[ \text{The ongoing primary stability studies will be monitored through} \]

\[ \text{months. Additionally, the first three} \]

\[ \text{commercial production batches of each strength will be monitored for stability through} \]

\[ \text{months in} \]

\[ \text{accordance with the post approval stability protocol and commitment.} \]

Drug Substance. Donepezil hydrochloride is a very well characterized drug substance (NDA 20-690) of noticeable stability. No detectable degradation was observed in various containers like: bags, glass bottles or tubes. Similarly donepezil was studied in acidic, basic and neutral conditions showing no degradation. Only in extremely harsh conditions of high temperature and oxidation a slight degradation was observed.

B. Description of How the Drug Product is Intended to be Used

Aricept RDT is provided in two strengths of 5 mg and 10 mg marketed in peelable blisters only. A film/aluminum foil, unit dose blister of peelable type consisting of 30 tablets will be packaged in an aluminum pouch. All packaging components are suitable for pharmaceutical or food contact use.
The standard room temperature storage is recommended and the requested expiration date of 24 months is justified.

C. Basis for Approvability or Not-Approval Recommendation

A stable formulation and a proven stability of API. The API and drug product specifications justified. The Establishment Evaluation System still shows two of the listed facilities scheduled for inspection as of 25-AUG-2004. The RFI of 17-JUN-04 produced response on 11-AUG-04, which addresses the total levels of impurities/degradants in the drug product. Therefore, at present the application has to be recommended as APPROVABLE subject to establishment evaluation and establishment of proper (Orally instead Rapidly) name for the drug product.

III. Administrative

Chemist: W. Janusz Rzeszotarski, Ph.D./25-AUG-2004
ChemistryTeamLeader/ Date: Maryla E. Guzewska, Ph.D.
Project Manager / Date: Melina Griffis, R.Ph
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-720

SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE
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ORIGINAL | 17-DEC-03 | 18-DEC-03 | 05-JAN-04
Amendment (BC) | 01-MAR-04 | 02-MAR-04 | 08-MAR-04
Amendment (BC) | 04-MAR-04 | 05-MAR-04 | 12-MAR-04
Amendment (BC) | 17-MAY-04 | 18-MAY-04 | 23-MAY-04
Amendment (BC) | 11-AUG-04 | 12-AUG-04 | 17-AUG-04

NAME & ADDRESS OF APPLICANT:
Eisai Medical Research Inc.
500 Frank W. Burr Blvd
Teaneck, NJ 07666

DRUG PRODUCT NAME
Proprietary: Aricept (donepezil hydrochloride) RDT
Nonproprietary/USAN: Donepezil hydrochloride
Code Name/#: AChEsterase Inhibitor/2013060
Chem.Type/Ther.Class:

PHARMACOL.CATEGORY/INDICATION:
AD

DOSE FORM:
Rapidly Disintegrating Tablets

STRENGTHS:
5 mg & 10 mg

ROUTE OF ADMINISTRATION:
Oral

DISPENSED:
XXXXX Rx_________OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
IUPAC name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl][methyl]-1H-inden-1-one HCl
CAS name: (±)-2-[[1-benzyl-4-piperidyl][methyl]-5,6-dimethoxy-1-indanone hydrochloride
Molecular formula: C_{29}H_{38}N_{2}O_{5}HCl
Relative molecular mass: Mr = 415.95
CAS Registry number: 142057-77-0

SUPPORTING DOCUMENTS: NDA 20-690 (Aricept Tablets)

RELATED DOCUMENTS: none

REMARKS/COMMENTS: Aricept RDT (Rapidly Disintegrating Tablets) are tablets containing 5 or 10 mg of donepezil hydrochloride. The application refers to the approved NDA 20-690 for the information on donepezil hydrochloride drug substance. The manufacturer, the method of manufacture and the specifications for the drug substance have not been changed. The need for the rapidly disintegrating tablet designed for the AD patients is well justified (impaired salivation, coordination and swallowing). The tablet manufacturing technique is well established and proven for other similar drug products (Risperdal M-Tabs, Claritin RediTabs, Zubrin, etc.). The 5 mg and 10 mg investigational formulations used in the bioequivalence studies and the proposed commercial formulations are the same.

CONCLUSIONS & RECOMMENDATIONS: The sponsor provided satisfactory data to prove the reproducibility of manufacturing process and the purity and stability of the drug product. The Establishment Evaluation System shows two of the listed facilities still scheduled for inspection as of 28-AUG-2004. The RFI response (see the attached E-mail) has to address the total of impurities present. Therefore, at present, the application has to be recommended as APPROVABLE subject to establishment evaluation and RFI response.

cc: Orig. NDA 21-720
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MGriffis
HFD-120/MEGuzewska
R/D Init by: MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: F:\msword\N21720R.002.doc
25 Page(s) Withheld

☑ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling
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/s/

Janusz Rzeszotarski
8/26/04 09:08:50 AM
CHEMIST

Maryła Guzewska
8/26/04 09:22:53 AM
CHEMIST