

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022568**

**CHEMISTRY REVIEW(S)**

# **NDA 22-568**

**Aricept (Donepezil HCl) Tablets, 23 mg**

**Eisai Medical Research Inc.**

**Akm Khairuzzaman, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division I/Branch I**

**Reviewed for the Division of Neurology Products, HFD-120**

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# Chemistry Review Data Sheet

1. NDA 22-568
2. REVIEW #: 1
3. REVIEW DATE: 21-July-2010  
Revised:
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	24-Sept-2009

7. NAME & ADDRESS OF APPLICANT:

<b>Name</b>	Eisai Medical Research
<b>Address</b>	300 Tice Boulevard Woodcliff Lake, NJ 07677, USA.
<b>Representative</b>	Kevin McDnald, Assistant Director, Reg. Affairs
<b>Telephone</b>	(201) 627-2292
<b>FAX Number</b>	(201) 949-4915

8. DRUG PRODUCT NAME/CODE/TYPE:

<b>Proprietary Name</b>	Aricept
<b>Non-Proprietary Name (USAN)</b>	Donepezil Hydrochloride
<b>Code Names</b>	E2020- <span style="background-color: #cccccc;">(b) (4)</span>
<b>Chemistry Type</b>	5
<b>Submission Priority</b>	S

## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Acetylcholinesterase Inhibitor
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 23 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx        OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

       SPOTS product – Form Completed

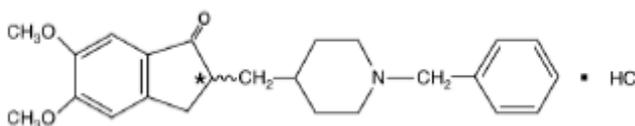
  X   Not a SPOTS product

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

Chemical Names: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidiny]methyl]-1H-inden-1-one HCl

US Adopted Name (USAN): Donepezil HCl

Laboratory Codes: N/A



Chemical Formula:  $C_{24}H_{29}NO_3 \cdot HCl$

Molecular Weight: 415.96

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	IV		(b) (4)	4	Adequate	03-May-2010 (Akm Khairuzzaman)
	III		4	Adequate	29-April-2002 (Raymond P. Frankewich)	
	III		4	Adequate	13-Apr-2009 (Yong-de Lu)	
	III		4	Adequate	22-Dec0-2008 (Craig M Bertha)	
	III		4	Adequate	12-Mar-2009 (Kurtyka, Bogdan)	
	III		4	Adequate	02-Dec-2009 (Yubing Tang)	
	III		4	Adequate	15-May-2000 (Rhee, Moo Jhong)	

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020-690	Donepezil IR tablets
IND	035,974	This IND was for Clinical development submitted on April 2005

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	19-Jul-2010	E. JOHNSON, HFD-320
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman
Biopharmaceutics	Dissolution methods: Acceptable	02/04/2010	Houda Mahayni
Biopharmaceutics	Extended release designation: <b>Not Acceptable</b>	04/02/2010	Patrick J Marroum

# The Chemistry Review for NDA 22-568

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Aricept® (donepezil hydrochloride) is approved in the United States for the treatment of Alzheimer's disease that is available in the market as immediate as well as orally disintegrating tablets in 5 mg and 10 mg strengths. This new drug application (22-568) was for the same drug but at a higher dose of 23 mg. (b) (4)

(b) (4) . As a result the sponsor finally has changed their product name in the label and package insert as “Aricept Tablets, 23 mg” in addition to their lower strengths, 5 mg and 10 mg tablets.

The chemistry, manufacturing and control (CMC) information of this application was sufficient to make a quality and safety decision on the product. For the drug substance or API, the sponsor has referenced their earlier approved applications (NDA # 20-690 and NDA # 21-720) and used the same drug substance with same specification in this product as well. Therefore, there was no concern found with the API used in this product. On the other hand, the drug product formulation is qualitatively and quantitatively very different than the marketed lower strengths of Aricept (b) (4)

(b) (4) the formulation composition, dissolution specification and the drug release mechanism will however remain unchanged and the product would be considered just as a conventional higher strength in addition to its marketed lower strengths. All new excipients used in this product formulation were found to be physically and chemically compatible with the API. Based on the prior knowledge with the same product (lower strengths), the drug product was manufactured (b) (4)

A risk assessment for the manufacturing process was performed at the initial stage of the product development and linked with the critical quality attributes of the finished product. Such risk assessment for the manufacturing process was then performed using commercial size batches and established the critical process parameters (CPP) at different risk level (level 1, 2 and 3) considering level 1 as a high risk level. The drug product has acceptable specification and showed good stability during the period tested. However, no design space or process model was submitted in this application.

## Executive Summary Section

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

In summary, the CMC reviewer found that the level of information and scientific data provided in this application and in the information amendment was sufficient to support the approvability of this product as “Aricept (Donepezil Hydrochloride) Tablets, 23 mg” from the point of chemistry, manufacturing and control.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

There are no Phase 4 commitments.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Aricept® (donepezil hydrochloride) is approved in the United States for the treatment of Alzheimer's disease. Currently it is available as immediate release (IR) products (NDA 20-690) and an ODT (orally disintegrating tablet, NDA 21-720) in the market. A solution under the NDA 20-719 was also approved but it was not marketed. Both the IR tablets and ODT are available in 5 mg and 10 mg strengths.

Under this NDA, Eisai Medical Research has developed a (b) (4) formulation (b) (4)

The strength of the developed product is 23 mg. (b) (4)

therefore the applicant has submitted the current NDA under 505(b)(1).

#### Drug Substance

Donepezil hydrochloride is a chemically-synthesized small molecule, piperidine-based acetylcholine esterase (AChE) inhibitor. It is a well characterized molecule with molecular formula  $C_{24}H_{29}NO_3 \cdot HCl$  and molecular weight 415.96. The chemical name is ( $\pm$ )-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one HCl. The bulk drug substance is a white crystalline powder with a bitter taste. It is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane. (b) (4)

The bulk drug substance is manufactured under NDA 20-690, which is cross-referenced for CMC information. Information in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 20-690.

## Executive Summary Section

Drug Product

The drug product is an (b) (4) formulation containing 23 mg of the active ingredient in its (b) (4) tablets with a film coat on the top (b) (4)

. Other excipient used in the finished product is similar to that of IR products which is already marketed in US. (b) (4)

The tablet presentation is a round, biconvex, brownish-red film-coated tablet debossed "Aricept" on one side and "23" on the other side.

The proposed commercial donepezil HCl (b) (4) tablet formulation is identical to the formulation used in the pivotal clinical trial under IND 35,974 and is manufactured at the same site. The only differences between the clinical tablets, primary stability batches, and proposed commercial image are the details of the tablet debossing.

The NDA stability package includes long-term stability data through 24 months and accelerated data through 6 months for commercial-scale batches. The shelf life proposed is (b) (4). However, based on the long term data provided a 24 months of shelf life can be granted at this time.

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

Aricept<sup>®</sup> Tablets, 23 mg is for oral administration for the treatment of moderate to severe dementia of the Alzheimer's type. Based on the clinical studies, the proposed package insert says that the patients who have been established on 10 mg/tab donepezil hydrochloride with good tolerability can be administered one Aricept<sup>®</sup> Tablets, 23 mg tablet once daily.

**C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (22-568) can be approved from the perspective of chemistry, manufacturing, and controls.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

/s/ A. Khairuzzaman, Ph.D.

**B. Endorsement Block**

Chemistry Reviewer:  
Pharmaceutical Assessment Lead:  
Branch Chief:  
Project Manager:

Akm Khairuzzaman, Ph.D.  
Martha Heiman, Ph.D.  
Ramesh Sood, Ph.D.  
Don Henry

**C. CC Block**

Orig. NDA 22-568  
HFD-120/Division File

71 pages have been withheld in full immediately following this page as B4 (CCI/TS).

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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AKM KHAIRUZZAMAN

07/21/2010

This NDA can be approved from CMC perspective.

RAMESH K SOOD

07/21/2010

Initial Quality Assessment  
Branch I  
Pre-Marketing Assessment Division I

**OND Division:** Division of Neurology Products  
**NDA:** 22-568  
**Applicant:** Eisai Medical Research  
**Stamp Date:** 24-Sep-2009  
**PDUFA Date:** 24-Jul-2010  
**Trademark:** (b) (4)  
**Established Name:** donepezil hydrochloride  
**Dosage Form:** (b) (4)  
**Route of Administration:** Oral  
**Indication:** Alzheimer's disease

**PAL:** Martha R. Heimann, Ph.D.

	Yes	No
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

## Summary and Critical Issues:

### Summary

Aricept® (donepezil hydrochloride) is marketed for treatment of Alzheimer's disease. Currently, there are two approved immediate release products available, a conventional compressed tablet (NDA 20-690) and an orally disintegrating tablet (NDA 21-720). An oral solution is approved under NDA 20-719, but is not marketed. Both approved tablet formulations are available in 5 mg and 10 mg strengths. The recommended dose is 5 mg or 10 mg donepezil HCl daily

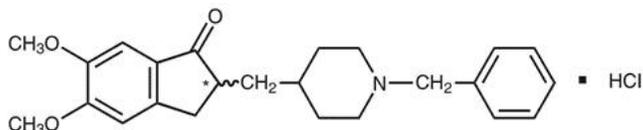
The current NDA provides for a donepezil hydrochloride extended release tablet formulation to be available in a single strength, 23 mg, for once daily administration. The product is intended to be used by patients who have been established on 10 mg of donepezil hydrochloride daily with good tolerability. Support for the 23 mg/day dose of the extended release product is based on a showing of superiority to 10 mg/day of the immediate release product in clinical trials.

### The Drug Substance

The active ingredient in (b) (4), donepezil hydrochloride (chemical name: (±)-2,3-dihydro-5, 6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride), is a reversible inhibitor of the enzyme acetylcholinesterase. It is a well characterized small molecule with molecular formula C<sub>24</sub>H<sub>29</sub>NO<sub>3</sub>•HCl and molecular weight 415.96. Donepezil HCl is a white crystalline powder with a bitter taste. It is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in

acetonitrile and practically insoluble in ethyl acetate and in n-hexane. (b) (4)

The chemical structure of donepezil HCl is:



The bulk drug substance is manufactured under NDA 20-690, which is cross-referenced for CMC information. Information in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 20-690.

Drug Product

The proposed dosage form is an (b) (4) tablet containing 23 mg of donepezil HCl in a (b) (4). The tablet presentation is a round, biconvex, brownish-red film-coated tablet debossed "Aricept" on one side and "23" on the other side. The components and composition of (b) (4) are summarized in the applicant's Table 2, which is shown below.

**Table 2 Composition of Aricept (b) (4) Tablets**

Component	Amount per Tablet (mg)	Function	Specification Reference
			US

(b) (4)

Tablet components are commonly used as excipients in solid oral dosage forms. All components comply with compendial (USP/NF) requirements or are manufactured from compendial excipients. Qualitative formulation information for the (b) (4) coating is provided in the submission; the manufacturer's DMF is cross-referenced for additional information.



The proposed commercial donepezil HCl extended release tablet formulation is identical to the formulation used in the pivotal clinical trial under IND 35,974 and is manufactured at the same site. The only differences between the clinical tablets, primary stability batches, and proposed commercial image are the details of the tablet debossing as summarized in the applicant's Table 8. Comparative dissolution profiles to support the change in debossing are provided in Module 3.2.P.2.2.1.2.

**Table 8 Summary of Debossment for Aricept (b) (4) 23 mg Tablets**

The content of Table 8 is completely redacted with a solid grey fill. The redaction covers the entire table area. In the top right corner of this redacted area, the text "(b) (4)" is visible.

Donepezil HCl (b) (4) tablets will be manufactured by Eisai at the firm's Kawashima facility in Japan and packaged at the firm's facility in Research Triangle, NC. (b) (4)

The proposed regulatory specifications for (b) (4) are shown on the following page. The proposed analytical procedures are relatively straight-forward. Donepezil HCl *Assay*, *Related substances*, *Content uniformity* and *Identity* are determined using a single reverse phase HPLC method [C18 column with water/ acetonitrile/ perchloric acid/ sodium decanesulphonate (650:350:1:2.4, v:v:v:w) mobile phase, UV detection at 271 nm]. Dissolution is determined using USP Apparatus II at 50 rpm in pH 6.8 phosphate, with sampling at 1, 3, and 8 hours. Dissolution results are quantitated by UV assay.

**Table 1 Specification for Aricept (b) (4) Tablets**

Test	Acceptance Criteria	Test Procedure
Description	Red, round biconvex debossed film coated tablet	Visual inspection 3.2.P.5.2.1 Description
Identification <sup>b</sup> (1)HPLC (2)UV	Conforms to retention time of the standard peak Absorption maxima: 266 to 270 nm, and 311 to 315nm	(1) HPLC 3.2.P.5.2.2 Identification HPLC (2) UV 3.2.P.5.2.3 Identification UV
Dissolution	Per Acceptance Table 2, USP <711> Dissolution: 1 hr: Between 10% and 30% 3 hr: Between 40% and 60% 8 hr: Not less than 80%	Apparatus 2 3.2.P.5.2.4 Dissolution
Related substances ER-35581 HCl Individual unspecified Total	(as % of drug substance) Not more than (b) (4) Not more than (b) (4) Not more than (b) (4)	HPLC 3.2.P.5.2.5 Assay & Related Substances
Assay (HPLC)	95.0–105.0% of the stated content (b) (4)	HPLC 3.2.P.5.2.5 Assay & Related Substances
Loss on drying <sup>a</sup>	Not more than (b) (4)	Weight measurement
Uniformity of dosage units <sup>b</sup>	Meets the requirements of USP <905>	HPLC 3.2.P.5.2.6 Content Uniformity
Microbial limit <sup>c</sup> Total aerobic microbial count: Total combined yeasts/mould count: <i>Escherichia coli</i> : <i>Staphylococcus aureus</i> : <i>Pseudomonas aeruginosa</i> :	Not more than (b) (4) Not more than (b) (4) Negative Negative Negative	Microbial test 3.2.P.5.2.7 Microbial Limits

<sup>a</sup> Acceptance criteria of loss on drying was tightened from (b) (4) after obtaining 6 months formal stability data.  
<sup>b</sup> Performed at release only.  
<sup>c</sup> Microbial limit tests are not routinely tested for release (First 3 production batches will be tested, then a testing regime of 1 batch tested per year will be adopted).

The NDA stability package includes long-term stability data through 12 months and accelerated data through 6 months for three commercial-scale batches. All batches were manufactured and packaged at the proposed commercial facilities. A 24-month shelf life is proposed.

**Critical issues for review**

*Drug Substance:* The effect of drug substance particle size was examined by the firm and is stated to be non-critical. This is considered a matter for review. No other issues can be identified based on information provided in the NDA.

*Drug Product:* No critical issues were identified during the initial assessment. The following issues are noted.

- (b) (4)
- (b) (4)

-  (b) (4)

### **Additional issues**

*Administrative:* The  (b) (4) is a new dosage form and approval of this application may be expected to increase use of the active moiety, donepezil hydrochloride. The firm has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

*Establishment Evaluation:* A full list of facilities involved in the manufacture, packaging and testing of  (b) (4) is provided in the submission. The facilities listed in Attachment 1 were entered into EES on 06-Oct-2009.

*Labeling/Established Name:* The active ingredient in  (b) (4), donepezil hydrochloride, is the hydrochloride salt and labeled potency is based on content of the salt. Therefore, there is no issue of consistency between the established name  (b) (4) and the labeled potency.

### **Comments for 74-Day Letter**

There are no comments for the 74 day letter.

### **Review, Comments and Recommendation:**

The NDA is fileable from a CMC perspective.

The drug substance is manufactured under an approved NDA. The  (b) (4) formulation is relatively simple and there are no QbD aspects to the submission. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team should be consulted for review of the dissolution method/acceptance criteria and data to support the change in debossing from the clinical tablets to the commercial image

Martha R. Heimann, Ph.D.  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

Ramesh Sood, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

**ATTACHMENT 1**

**Manufacturing Establishment for Aricept <sup>(b) (4)</sup> Tablets**

<b>Facility Information</b>	<b>Function</b>
<p>Eisai Co., Ltd. Kashima Plant 22 Sunayama Kamisu-shi Ibaraki-ken 314-0255 Japan</p> <p>FEI: 3002806886 Contact: Kazuo Guro, Manager QA Dept. Tel.: 81-479-46-1157 Fax.: 81-479-46-4969</p>	<p>(b) (4)</p>
<p>Eisai Co., Ltd. 1 Kawashimatakehaya-machi Kakamigahara-shi Gifu-ken 501-6195 Japan</p> <p>FEI: 3004967045 Contact: Ryusuke Sasaki, Director QA Dept. Tel.: 81-586-89-4706 Fax.: 81-586-89-5291</p>	
<p>Eisai, Inc. (RTP Campus) 900 Davis Drive Research Triangle Park, NC 27709 USA</p> <p>FEI: 3001753294 Contact: Lynn Poplin, Director Quality Systems Tel.: 919-941-7282 Fax.: 919-941-0660</p>	

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA Numbers: 22-568**

**Applicant:** (b) (4)

**Stamp Date: 21-Aug-2009**

**Drug Name: Donepezil HCl extended release tablets**

**NDA Type: Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA

Date

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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MARTHA R HEIMANN  
10/06/2009

RAMESH K SOOD  
10/13/2009