DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022568 **NDA APPROVAL**

Eisai Inc.
Attention: Martina Struck, Ph.D.
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Dr. Struck

Please refer to your New Drug Application (NDA) dated September 24, 2009, received September 24, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aricept (donepezil hydrochloride) 23mg Tablets.

We acknowledge receipt of your amendments dated:

10/6/2009	1/7/2010	1/22/2010	1/25/2010
2/22/2010	5/27/2010	6/03/2010	7/01/2010
7/06/2010	7/22/2010		

This new drug application provides for the use of Aricept (donepezil hydrochloride) 23 mg Tablets for the treatment of moderate to severe dementia of the Alzheimer's type.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on July 22, 2010 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022525**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are not feasible (the disease does not occur in children).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following serious risks:

- A signal of the serious risk of neurodegeneration observed in adult rat brain when donepezil was coadministered with memantine, identified in a published report by Creeley et al. (*Neurobiology of Aging* 29: 153-167, 2008);
- The potential for an unexpected serious risk of adverse events due to increased exposure to CYP2B6, 2C8 and 2C19 substrates, if donepezil is an inhibitor of these CYP enzymes and is co-administered with these substrates. The inhibition potential of donepezil on CYP2B6, CYP2C8, and CYP2C19 was not well characterized in the NDA.
- The potential for an unexpected serious risk of increased exposure to donepezil, which may result in safety issues, if donepezil is a P-gp substrate and is co-administered with P-gp inhibitors. There are several recent publications by Summerfield et al. (*J Pharmacol Exp Ther.* 2007 Jul;322(1):205-13), Wager et al. (*ACS Chem Neurosci.* 2010, 1, 420-

434), Yoshihiro (*Drug Metab Rev.* 2005 Nov; 37 (suppl 2): 177-178), and Ishiwata et al. (*J Nucl Med.* 2007 Jan;48(1):81-7) showing conflicting results that were not analyzed or reported according to recommendations provided in the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf. Whether donepezil is a substrate for the transporter P-glycoprotein (P-gp) was not well characterized in the NDA.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1662 – 1 A Single-Dose Oral Neurotoxicity Study in Female Rats

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.

The timetable you submitted on July 8, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/31/2010
Study Completion:	12/31/2011
Final Report Submission:	06/30/2012

PMR 1662-2 An *in vitro* study to evaluate the potential of donepezil as an inhibitor of CYP2B6, CYP2C8, and CYP2C19.

The timetable you submitted on July 8, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/31/2010
Study Completion:	6/30/2011
Final Report Submission:	12/31/2011

PMR 1662-3 **An *in vitro* study to evaluate whether donepezil is a P-glycoprotein substrate.**

The timetable you submitted on July 8, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/31/2010
Study Completion:	6/30/2011
Final Report Submission:	12/31/2011

Submit clinical protocols to your IND 35,974 for this product, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

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

/s/

RUSSELL G KATZ
07/23/2010