

**TRANSMITTED BY FACSIMILE**

Gary Wieczorek, Associate Director, Regulatory Affairs
Eisai Medical Research Inc.
300 Tice Blvd
Woodcliff Lake, NJ 07677

RE: NDA # 20-690
Aricept (donepezil hydrochloride) Tablets
MACMIS #18244

Dear Mr. Wieczorek:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two consumer broadcast television ads (TV ads) for Aricept[®] (donepezil hydrochloride) Tablets ("Beach" (ARU00435) and "Garden" (AAR00036)) submitted by Eisai Medical Research Inc. (Eisai) under cover of Form FDA-2253. The TV ads are misleading because they overstate the efficacy of the drug. Thus, the TV ads misbrand Aricept in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n), and FDA implementing regulations. 21 CFR 202.1(e)(5)(i) & (e)(6)(i).

Background

According to its FDA-approved product labeling (PI), Aricept is indicated for "the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild to moderate Alzheimer's Disease, as well as in patients with severe Alzheimer's Disease."

According to the CLINICAL PHARMACOLOGY section of the PI, Aricept was tested in mild to moderate Alzheimer's disease in two randomized, double-blind, placebo-controlled studies (the Fifteen-Week and Thirty-Week Studies). In each study, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) was used. This subscale is a multi-item instrument that examines selected aspects of cognitive performance, including elements of memory, orientation, attention, reasoning, language, and praxis. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores (scored from 0 to 70) for Aricept-treated patients compared to placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. The Fifteen and Thirty week studies also analyzed Aricept's ability to produce an overall clinical effect using a Clinician's Interview Based Impression of Change that required the use of caregiver information (CIBIC plus). The CIBIC plus examined general, cognitive, and behavioral function and activities of daily living on a 7-point scale ranging from "markedly improved" to "markedly worse." The CIBIC plus results in the Thirty-Week Study (Figure 3 in the PI) are presented in the following graph:

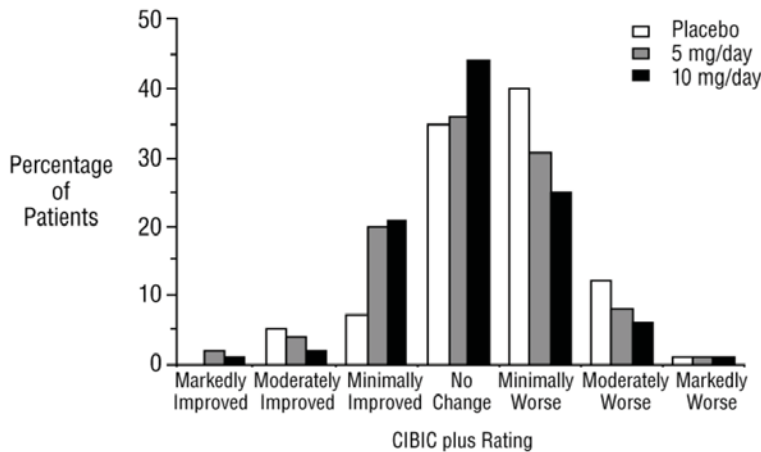


Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24

In patients with severe Alzheimer’s disease, the effects of Aricept on cognitive function were tested in a 24 week study (Japanese study), which evaluated patients on both the Severe Impairment Battery (SIB) and CIBIC plus. In addition, a randomized, double-blind, placebo-controlled clinical trial (the Swedish 24-Week Study) assessed cognitive function using the SIB and daily function using the Modified Alzheimer’s Disease Cooperative Study Activities of Daily Living inventory for Severe Alzheimer’s Disease (ADCS-ADL-severe), which is a subset of 19 items, including ratings of the patient’s ability to eat, dress, bathe, use the telephone, get around, and perform other activities of daily living. After 24 weeks of treatment, the mean difference in the ADCS-ADL-severe change scores (scored from 0 to 54) for Aricept-treated patients compared to placebo was 1.8 units. The following graph shows the effect of Aricept on ADCS-ADL-severe in the Swedish 24-week study (Figure 9 in PI):

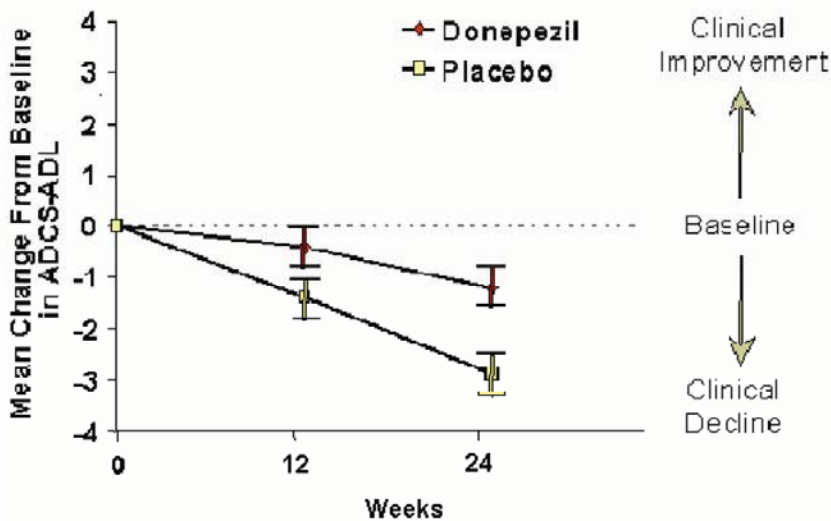


Figure 9. Time course of the change from baseline in ADCS-ADL-severe score for patients completing 24 weeks of treatment.

Aricept is contraindicated in patients with known hypersensitivity to the drug or to piperidine derivatives. Aricept is also associated with serious risks as reflected in the WARNINGS section of the PI, including syncopal episodes and gastrointestinal bleeding, especially in patients with a history of ulcers or in patients who are taking concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). The most common adverse reactions associated with Aricept in severe Alzheimer's disease are diarrhea, anorexia, vomiting, nausea, and ecchymosis. In mild to moderate Alzheimer's disease, the most common adverse reactions are nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The "Beach" TV ad presents an elderly man staring off into space, appearing distant, confused, and disinterested, while the rest of his family walks on the beach, and the man's daughter has a look of concern on her face. While this beach scene is taking place, the man's daughter makes the following statements:

- "Dad had been repeating things and acting disoriented for a while, like something was stealing him away from us."
- "We wanted to be there for him, to hold on to him." (While this statement is being made, a young boy clasps the man's hand.)

The ad then shows the man and his daughter discussing Aricept with his doctor. Specifically, the daughter states:

- "Dad's doctor said his symptoms were signs of Alzheimer's, a type of dementia, and that prescription Aricept could help." (While this statement is being made, the daughter poignantly clasps her father's hand.)

After the patient and his daughter discuss Aricept with the doctor, the man's behavior changes dramatically. The man is shown happily interacting with his family members, moving more quickly and with greater focus. For example, he pats his grandson on the head while pouring cereal, winks while feeding the dog under the table, energetically cheers and points at a soccer game while following the plays, and clasps his daughter's hand. While these scenes are taking place, the ad makes the following statements:

- "Studies showed Aricept slows the progression of Alzheimer's symptoms."
- "It improves cognition and slows the decline of overall function."
- "If it helps Dad be more like himself longer, that's everything to us."
- "Don't wait. Talk to your doctor about Aricept."

The "Garden" TV ad presents an elderly woman looking away from family members, appearing confused, aloof, and disoriented. While these scenes are taking place, the woman's daughter makes the following statements:

- “We’d been noticing mom acting forgetful and confused, like she was drifting away.”
- “We wanted to be there for her, to hold on to her.” (While this statement is being made, a young girl clasps the woman’s hand.)

Similar to the “Beach” ad, this ad then shows the woman and her daughter discussing Aricept with her doctor. Specifically, the ad states:

- “Studies showed Aricept slows the progression of Alzheimer’s symptoms.”
- “It improves cognition and slows the decline of overall function.”

After the woman and her daughter discuss Aricept with the doctor, the woman’s behavior changes dramatically. The woman is shown interacting happily with her daughter and her grandchildren, trying on a hat, helping them plant seeds, and working with them in the garden. At the end of the ad, the daughter looks at her mother, smiling and hugging her, and the woman clasps her daughter’s hand.

The totality of the above claims and presentations misleadingly overstates the efficacy of Aricept, implying a greater benefit than has been supported by substantial evidence or substantial clinical experience. As described above, the beginning segment of each ad presents patients with Alzheimer’s disease looking blank, confused, distant, and walking off apart from their family members. However, after talking to their doctors about treatment with Aricept, the patients are seen interacting and communicating with their family members, happily and actively involved in activities with them. These presentations imply that, as a result of Aricept treatment, patients’ cognitive and daily functioning, specifically aspects of attention and focus, orientation, communication, and social interaction and engagement, will be restored to normal.

The results from the Aricept efficacy trials in patients with mild to moderate and severe Alzheimer’s disease do **not** support such a drastic improvement. According to the CLINICAL PHARMACOLOGY section of the PI, the mean differences in the ADAS-cog change scores for Aricept-treated patients compared to placebo were **only 2.8 and 3.1 units** (scored from 0 to 70) for the 5 mg/day and 10 mg/day treatments, respectively, after 24 weeks of treatment. Furthermore, the distribution of CIBIC plus scores in patients in the Thirty-Week Study (see Figure 3 in Background section) indicates that **less than 5%** of patients treated with Aricept at either dose were “markedly improved” or “moderately improved.” The majority of patients experienced no change or became worse on Aricept treatment. Moreover, Figure 9 (see Background section) indicates that although the Aricept-treated group in the Swedish 24-Week Study reached a statistically significant result in change from baseline in ADCS-ADL-severe scores versus placebo, the mean difference was **only 1.8 units** (scored from 0 to 54), and patients on Aricept continued to show clinical decline over time.

Therefore, the claims and presentations in both TV ads are **not** representative of the results from the clinical trials for Aricept, and misleadingly overstate the efficacy of the drug. The inclusion of the superimposed text, “Individual results may vary,” does not mitigate these misleading presentations.

Conclusion and Requested Action

For the reasons discussed above, the TV ads misbrand Aricept in violation of the Act, 21 U.S.C. 352(n), and FDA implementing regulations. 21 CFR 202.1(e)(5)(i) & (e)(6)(i).

DDMAC requests that Eisai immediately cease the dissemination of violative promotional materials for Aricept such as those described above. Please submit a written response to this letter on or before February 18, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Aricept that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 18244 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Aricept comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sharon M. Watson, PharmD
LCDR, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-20690	----- ORIG-1	----- EISAI INC	----- ARICEPT

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

/s/

SHARON M WATSON
02/03/2010