



NOV 6 2012

Sidney M. Wolfe, M.D.  
• Director, Health Research Group  
Public Citizen  
1600 20<sup>th</sup> St., NW  
Washington, DC 20009

Re: Docket No. FDA-2011-P-0455

Dear Dr. Wolfe,

This responds to your petition dated May 18, 2011 (Petition), in which you request that the Food and Drug Administration (FDA or Agency) (1) withdraw from the market Aricept (donepezil hydrochloride) 23 milligram (mg) tablets (Aricept 23) and (2) add a warning to the labeling for Aricept (donepezil hydrochloride) 5 mg and 10 mg tablets (Aricept 5 and Aricept 10, respectively) that contraindicates the use of 20 mg per day. You claim that Aricept 23 is not effective, has significantly increased adverse events compared to Aricept 10, and received negative reviews from the FDA clinical and statistical reviewers (Petition at 1). We have considered your Petition carefully, and, for the reasons that follow, your Petition is denied.

## I. BACKGROUND

### A. Aricept (donepezil)

Eisai Inc. (Eisai) is the holder of new drug application (NDA) 22568 for Aricept 23, which was approved on July 23, 2010. Aricept 23 is an acetylcholinesterase inhibitor indicated for the treatment of moderate to severe dementia of the Alzheimer's type (AD).<sup>1</sup> Aricept 5 and Aricept 10 were approved on November 25, 1996, in a separate new drug application, NDA 020690, also held by Eisai. Aricept 5 and Aricept 10 originally were indicated for the treatment of mild to moderate AD, but an indication for the treatment of severe AD was added to Aricept 10 in 2006.<sup>2</sup>

AD is a neurodegenerative disorder that causes progressive loss of brain function, dementia, and, ultimately, death. Most diagnosed sufferers are over the age of 65, although early-onset AD may strike patients decades earlier.<sup>3</sup> An estimated 5.4 million

<sup>1</sup> Aricept 23 labeling is available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020690s035\\_021720s008\\_022568s0051bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035_021720s008_022568s0051bl.pdf).

<sup>2</sup> See Approval Letter, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2006/020690s026\\_021720s003LTR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/020690s026_021720s003LTR.pdf).

<sup>3</sup> See [http://www.alz.org/alzheimers\\_disease\\_early\\_onset.asp](http://www.alz.org/alzheimers_disease_early_onset.asp).

people in the United States have AD,<sup>4</sup> and this number is expected to rise as the so-called “Baby Boomer” generation ages.

There is no cure for AD, and its pathology is still poorly understood. Therapies for AD are few; only two classes of drugs (cholinesterase inhibitors and memantine) have been FDA-approved for AD treatment. For patients with severe AD, the only approved treatments are memantine and donepezil hydrochloride (donepezil).

## **B. Aricept 23 Clinical Trial**

In support of its Aricept 23 NDA, Eisai submitted the results of a single double-blind clinical trial, Study 326, which compared the safety and efficacy of Aricept 23 against Aricept 10 in treating moderate to severe AD. Study participants were patients in 23 countries, including the United States, who had moderate to severe AD, and who already had been taking Aricept 10 daily for at least 3 months. The study did not have a placebo control arm; instead, study subjects randomly were assigned to take either Aricept 10 or Aricept 23 once a day.

Study 326 had two co-primary endpoints: Severe Impairment Battery (SIB) scores, which measure cognitive function,<sup>5</sup> and Clinician Interview-Based Impression of Change-Plus (CIBIC+) scores, which measure overall patient functioning (i.e., “general [functioning], mental/cognitive state, behavior, and activities of daily living”<sup>6</sup>). Study 326 also had two secondary endpoints, which were intended to be used in support of the co-primary endpoints: Alzheimer’s Disease Cooperative Study — Activities of Daily Living (ADCS-ADL) scores, which measure a patient’s ability to accomplish activities of daily life,<sup>7</sup> and Mini-Mental State Examination (MMSE) scores, which measure cognitive functioning.<sup>8</sup> Patients were assessed at baseline (i.e., before the assigned dosing began) and periodically throughout the course of the 24-week study. Their SIB, CIBIC+, ADCS-ADL, and MMSE scores at baseline and at week 24 were compared to determine how their conditions changed over the course of the study. The changes in scores were then compared to determine the extent to which each patient group (i.e., the Aricept 10 group or the Aricept 23 group) improved or deteriorated relative to the other group.<sup>9</sup>

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<sup>4</sup> [http://www.alz.org/downloads/Facts\\_Figures\\_2011.pdf](http://www.alz.org/downloads/Facts_Figures_2011.pdf).

<sup>5</sup> Aricept Labeling, p. 11.

<sup>6</sup> Medical Review, p. 24, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022568Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf).

<sup>7</sup> Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer’s disease. The Alzheimer’s Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S33-9. ADCS-ADL scores evaluate the primary domain assessed by the CIBIC+ test. Reisberg B. Global measures: utility in defining and measuring treatment response in dementia. *Int Psychogeriatr* 2007;19:421-455.

<sup>8</sup> See, e.g., Schmitt FA, Cragar D, Ashford W, Reisberg B, Ferris S, Mobius H-J, and Stoffler A. Measuring cognition in advanced Alzheimer’s disease for clinical trials. *J Neural Transm* 2002; (Suppl) 62:135-148.

<sup>9</sup> A higher score on either the SIB or CIBIC+ assessment denotes a higher level of functioning.

The final protocol called for the use of an analysis of covariance (ANCOVA)<sup>10</sup> statistical model for the SIB assessment,<sup>11</sup> and a non-parametric ANCOVA statistical model with a Cochran-Mantel-Haenszel component for the CIBIC+ assessment.<sup>12</sup> For both of the primary endpoints, “[i]f a patient [was] missing a Week 24 observation, then the last observed value would be carried forward and used as the endpoint observation for the change from baseline analysis[.]”<sup>13</sup> The secondary endpoints were assessed using the same statistical model as used in the SIB assessment, including the use of the LOCF values for intent-to-treat<sup>14</sup> patients who lacked week 24 scores. The protocol stated that a “positive” study result required statistically significant improvements (i.e.,  $p < 0.05$ )<sup>15</sup> in both SIB and CIBIC+ measurements for patients treated with Aricept 23 when compared to patients treated with Aricept 10. Study results will be discussed in detail in section II, below.

### C. NDA Approval Standards

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a sponsor seeking to market a new drug submit an NDA or abbreviated new drug application (ANDA). NDAs are submitted under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)) and approved under section 505(c) of the FD&C Act (21 U.S.C. 355(c)). NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the labeling (21 CFR 314.50(d)(5)(viii)). Furthermore, applicants must not only provide substantial evidence of effectiveness for claimed indications in their applications, but also provide evidence to support the approved dosage and administration for the drug (21 CFR 314.50(d)(5)(v)). As stated in section 505(d) of the FD&C Act, “substantial evidence” means:

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<sup>10</sup> ANCOVA stands for the (parametric) analysis of covariance. By adjusting the analysis for a covariate variable (in this case, the measurement of the SIB at baseline, which is expected to be predictive of the SIB change at the end of the trial), this ANCOVA is expected to lead to a more efficient trial, i.e., getting the same amount of information from fewer subjects.

<sup>11</sup> Medical Review, p. 28. The SIB data analysis had “terms for baseline, country, and treatment.” Id. The CIBIC+ analysis “adjust[ed] for [Clinician Interview-Based Impression of Severity]-Plus score at baseline with a stratification adjustment for country.” Id.

<sup>12</sup> Statistical Review, p. 12, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022568Orig1s000StatR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000StatR.pdf). The Cochran Mantel Haenszel test, which is a nonparametric analysis of variance test, was used for the CIBIC+, because the CIBIC+ can only take on 7 distinct values, and a (parametric) ANCOVA is usually reserved for a continuous variable, i.e., a variable that can assume a large or unlimited number of possible values.

<sup>13</sup> Id. at 27. This is known as a *last-observation-carried-forward* (LOCF) analysis.

<sup>14</sup> The “intent to treat” population refers to:

all randomized subjects who are in the Safety Population and for whom either (a) SIB data are available at Baseline and at least one subsequent SIB data point is available post-Baseline, or (b) Clinician’s Interview-Based Impression of Severity (Plus Caregiver Input Version, CIBIS+) data are available at Baseline, and at least one subsequent CIBIC+ data point is available post-Baseline.

(Statistical Review, p. 10.)

<sup>15</sup> Medical Review at 28.

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Significantly, “[i]f the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence[.]”<sup>16</sup>

#### **D. Standard for Withdrawal of NDA Approval**

The FD&C Act establishes the standard upon which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA. Specifically, the Agency will withdraw approval of an NDA for safety or efficacy reasons if it finds:

- (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;
- (2) that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or
- (3) on the basis of new information before [the Agency] with respect to such drug, evaluated together with the evidence available to [the Agency] when the application was approved, . . . there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.<sup>17</sup>

## **II. DISCUSSION**

Your Petition asks that FDA (1) withdraw Aricept 23 from the market, and (2) add a warning to the labeling for Aricept 5 and Aricept 10, which would state that “use of 20

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<sup>16</sup> Section 505(d)(7) of the FD&C Act.

<sup>17</sup> Section 505(e) of the FD&C Act (21 U.S.C. 355(e)); see also 21 CFR 314.150. In addition, section 505(e) of the Act provides that if the Secretary of Health and Human Services “finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately.”

milligrams per day is counter indicated” (Petition at 13). For the reasons explained below, FDA denies your requests.

### **A. Efficacy of Aricept 23**

In support of your request for withdrawal, you state that the single clinical trial of Aricept 23 did not meet the efficacy criteria set forth by FDA for approval of dementia drugs generally and specifically for Aricept 23 (Petition at 1). Specifically, you state that Aricept 23 was not shown to be superior to Aricept 10 on both co-primary endpoints, the SIB and CIBIC+, in the trial. The efficacy results for Aricept 23 on the CIBIC+ were numerically superior to those for Aricept 10, but you are correct that this result was not statistically significant. However, the data did show highly statistically significant improvements on SIB scores for Aricept 23 when compared to Aricept 10. These results indicate that Aricept 23 is effective for its indicated use, and is more effective than Aricept 10 in improving cognitive function in patients with moderate to severe AD.

The original clinical trial endpoints (SIB and CIBIC+) were established because the sponsor told FDA that it would be submitting an application for a controlled-release (CR) drug containing 23 mg of donepezil. The pharmacokinetic (PK) characteristics of CR products and immediate-release (IR) products differ, and FDA typically does not know in advance what specific PK characteristics will be necessary to demonstrate that a CR drug is safe and effective. This is why the Agency often requests that clinical trials establish the effectiveness of a CR product, even when an IR formulation already has been approved. FDA agreed to the efficacy threshold for Aricept 23 to confirm that the CR form was effective, with the expectation that the drug would have release and absorption characteristics different from those of Aricept 5 and Aricept 10 (both of which are IR products).

However, after NDA 22568 was submitted and reviewed—and well after clinical trial parameters had been agreed upon by FDA and Eisai—it became apparent that Aricept 23 does not behave like a CR product. It had essentially the same PK data pattern as Aricept 5 and 10, both of which had already been deemed effective. Thus, for purposes of determining efficacy, it became less critical for Aricept 23 to show statistically significant superiority over Aricept 10 on both primary endpoints, as it was already known that a lower dose of essentially the same drug was effective. As will be discussed below, FDA often approves a higher dose of a drug when it is only numerically, but not statistically significantly, superior to lower doses. The fact that Aricept 23 showed statistically significantly improved SIB scores (and, for certain groups, CIBIC+ scores), provides a firm basis for the conclusion not only that Aricept 23 is effective for its indicated use, which would be expected given the effectiveness of 10 mg of the IR, but that it has greater effectiveness than the lower dose.

#### **1. SIB Data**

The SIB test is a measure of cognitive functioning. It assesses memory, language, orientation, attention, praxis, visuospatial ability, construction, and social interaction, and

is scored on a scale of 0 (worst) to 100 (best).<sup>18</sup> Over the 24-week course of Study 326, the Aricept 10 group showed an improvement of 0.4 points from baseline on a 100-point scale. The Aricept 23 group showed an improvement of 2.6 points on a 100-point scale. The 2.2 point difference between the Aricept 23 group and the Aricept 10 group was statistically significant with a p value of 0.0001,<sup>19</sup> a much stronger finding than the generally accepted statistical significance threshold of 0.05.

**a. Statistical Significance**

Your Petition acknowledges that the data from Study 326 demonstrated a statistically significant improvement in SIB scores for Aricept 23 patients over Aricept 10 patients (Petition at 3), but questions the strength of the SIB findings (Petition at 4). You base this challenge on the fact that 23% of the Aricept 23 data was missing in week 24 of the study, as compared to only 13% of data missing from the Aricept 10 group that same week (Petition at 4). You also noted that the Aricept 23 patients who dropped out of the study often did so earlier than the Aricept 10 patients who dropped out of the study (Petition at 4). The absence of actual week 24 data for dropout patients, however, did not prevent FDA statisticians from conducting thorough SIB data analyses—nor, in this case, do those analyses alter the conclusion that Aricept 23 is effective in improving measures of cognition for patients with moderate to severe AD.

FDA's statistical reviewer conducted several different analyses that each took missing data into account in different ways. The LOCF ANCOVA analysis, which was the analysis specified in the trial protocol to address the problem of missing data, assumed no change in SIB scores from the last pre-dropout SIB score to week 24.<sup>20</sup> This analysis resulted in the statistically significant value of  $p=0.0001$  (reflecting a 2.2-point SIB score improvement between Aricept 23 and Aricept 10 patients).<sup>21</sup> An observed cases (OC) ANCOVA analysis also was conducted. In that analysis, dropouts were ignored completely: their data was not accounted for at all; the analysis only assessed the scores of patients who completed the study. The OC ANCOVA analysis also resulted in a statistically significant value ( $p=0.0001$ ) (reflecting a 2.4-point SIB score improvement

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<sup>18</sup> See Aricept Labeling, p. 11.

<sup>19</sup> Id. Such a low p value is unusual, and represents a high level of statistical significance between the SIB score improvement of the Aricept 23 patients and the SIB score improvement of the Aricept 10 patients.

<sup>20</sup> This means that if Patient A dropped out after week 6, his or her projected "week 24" score would be the same as his or her actual week 6 score. Similarly, if Patient B dropped out after week 12, his or her projected "week 24" score would be the same as his or her week 12 score. In effect, it assumed that all dropout patients had stayed in the study, and that their SIB scores had not changed from the point at which they dropped out until the end of the study. The analysis then compared changes in the two patient populations from the baseline SIB scores (i.e., the patients' SIB scores prior to the first dose of either Aricept 23 or Aricept 10 in the study) to the week 24 SIB scores (either actual, in the case of patients who stayed in the study, or "last observed," for the patients who dropped out of the study).

<sup>21</sup> Statistical Review, p. 18. A Wilcoxon rank sum test using LOCF data also produced a statistically significant  $p=0.006$ . Id. at 23. The Wilcoxon test is based on the overall rankings of all patients' SIB changes from baseline at the endpoint. It compares the average rank of the SIB change from baseline at endpoint between the high and low dose groups. The test can be applied under various assumptions about the missing Week 24 SIB data and the result may change depending on the particular assumption used.



between Aricept 23 and Aricept 10 patients).<sup>22</sup> A third analysis, the mixed model repeated measures (MMRM) ANCOVA analysis, went even further than the OC ANCOVA analysis in its attempt to eliminate bias based on calculations of the missing scores.<sup>23</sup> It included dropout patient scores in a manner that retained the link between the SIB score and the study point (e.g., week 6, week 15, week 20) at which the scores were assessed.<sup>24</sup> The MMRM ANCOVA analysis showed a statistically significant difference in SIB scores, similar to the LOCF and OC ANCOVA analyses.<sup>25</sup> The agreement of the LOCF, OC, and MMRM ANCOVA analyses—each of which took a different approach toward missing data—provides further evidence that the cognitive improvements shown in Study 326 are, indeed, statistically significant, irrespective of the method used to impute missing data.

### **b. Clinical Significance**

Your Petition refers to the 2.2 point SIB score improvement between Aricept 23 and Aricept 10 patients as “very small” (Petition at 3), but this level of improvement is comparable to SIB improvements shown in other comparison studies of higher and lower doses of approved dementia drugs. For example, in one clinical trial, the difference in SIB score improvement between Aricept 5 and Aricept 10 patients also was 2.2 points.<sup>26</sup> In addition, in the Namenda (memantine hydrochloride) clinical trials, the SIB score improvement difference between the Namenda + donepezil patient group over the placebo + donepezil patient group was 3.3 points. FDA determined that this 3.3-point difference in SIB scores was substantial evidence of the drug’s efficacy and supported Namenda’s approval.<sup>27</sup> The increased benefit of Aricept 23 compared to Aricept 10 is thus similar to the increases in efficacy seen in comparisons of higher and lower doses of other approved dementia drugs.

As there was no placebo group in Study 326, we do not know the magnitude of the improvement that would have been seen in Aricept 23 patients compared to patients receiving placebo.<sup>28</sup> However, Aricept 10 already has been shown in clinical trials to be

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<sup>22</sup> Statistical Review, p. 18.

<sup>23</sup> It used the data set used in the OC analysis, but also included some patients who had dropped out at earlier points, and thus were excluded from the OC analysis because they did not have a week 24 SIB score. Thus, the MMRM analysis helped reduce bias over both the OC analysis (because it included dropout patients) and the LOCF analysis (because it took into account when the SIB measurements were taken).

<sup>24</sup> “This model adjusted for scheduled-visit and treatment-by-visit interaction in addition to the other effects included in the primary ANCOVA model. For the MMRM model the within-patient covariance structure was assumed to be as general as possible, i.e., ‘unstructured.’” Statistical Review, p. 23.

<sup>25</sup> Statistical Review, p. 23.

<sup>26</sup> See Review and Evaluation of Clinical Data for Supplemental NDA 20690, p. 82.

<sup>27</sup> See, e.g., [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/0214871bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/0214871bl.pdf). (Note that this is not the most current version of the drug labeling.)

<sup>28</sup> Dose-comparison concurrent control (e.g., Study 326) and placebo concurrent control are both recognized study designs described in FDA’s regulations pertaining to adequate and well-controlled studies (see 21 CFR 314.126(b)(2)(i)-(ii)). However, as the goal of the study was to demonstrate superiority of Aricept 23 over Aricept 10, Study 326 did not contain a placebo arm.

effective for treating patients with moderate to severe AD, and has been shown to improve SIB scores over placebo in this population.<sup>29</sup> Thus, the statistically significant improvement in SIB scores for Aricept 23 over Aricept 10 indicates that Aricept 23 is more effective than Aricept 10, and likely has a considerably larger effect than 2.2 points compared to placebo.

In sum, the Aricept 23 clinical trial shows that Aricept 23 has a statistically significant improvement on SIB scores when compared to Aricept 10. Such improvement in cognition, the principal manifestation of AD, supports FDA's determination that Aricept 23 is effective in treating patients with moderate to severe AD.

## 2. CIBIC+ Data

The CIBIC+ test measures such areas as "general [functioning], mental/cognitive state, behavior, and activities of daily living."<sup>30</sup> As your Petition notes (see Petition at 3), the overall CIBIC+ analysis did not show a statistically significant difference between the scores of the Aricept 10 and Aricept 23 patients when using the LOCF analysis of intent-to-treat population CIBIC+ scores, as specified in the protocol.<sup>31</sup> You imply that, consequently, Aricept 23 will not be effective in treating moderate to severe AD patients (Petition at 3-4).

In FDA's experience, it is not uncommon to see, and for the Agency to approve, dementia drugs that show evidence of efficacy, but for which some trials nevertheless did not show statistically significant improvements in CIBIC+ scores in direct comparisons between higher and lower doses of the drug. Aricept 10 demonstrates this: in studies in mild to moderate AD patients, both Aricept 5 and Aricept 10 had statistically significant differences in CIBIC+ scores when compared to placebo, but the difference in CIBIC+ scores between Aricept 5 and Aricept 10 was not statistically significant.<sup>32</sup> Nonetheless, the 10 mg dose was found to be effective for treatment of mild, moderate, and severe AD.

We thus have evidence from clinical trials that Aricept 10 is effective in treating patients with moderate to severe AD, with effects on both SIB and CIBIC+, and evidence that Aricept 23 has a statistically significantly increased effect on SIB scores over Aricept 10 in the same patient population. Moreover, in Study 326, the CIBIC+ values<sup>33</sup> in the Aricept 23 group were numerically (if not statistically significantly) superior to those in

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<sup>29</sup> See Aricept Labeling, pp. 9-11. In the Swedish study of severe AD patients taking Aricept 10 versus placebo, "[a]t 6 months of treatment, the mean difference in the SIB change scores for ARICEPT treated patients compared to patients on placebo was 5.9 points. ARICEPT treatment was statistically significantly superior to placebo." *Id.* at 10. A 24-week Japanese study of severe AD patients also showed a statistically significant improvement in SIB scores for Aricept 10 patients over placebo. *Id.* at 11.

<sup>30</sup> Medical Review, p. 24.

<sup>31</sup> Statistical Review, p. 20.

<sup>32</sup> See Aricept Labeling, p. 8.

<sup>33</sup> As discussed in section I.B and in the Aricept Labeling, both the CIBIC+ test and the modified ADCS-ADL assessed similar domains.



the Aricept 10 group.<sup>34</sup> When the results on both of the co-primary endpoints from Study 326 are viewed in tandem, it becomes evident that Aricept 23 offers an overall increased benefit to patients with moderate to severe AD when compared to the 10 mg dose. Aricept 23's approval is appropriate under the circumstances, and is consistent with FDA's past assessments of efficacy for dementia drugs; it is effective in treating patients with moderate to severe AD.

It is important to remember that the core cognitive deficits of AD invariably result in increasingly severe functional impairment over time. The decision to approve Aricept 23 stems, in considerable part, from the greater effect on SIB score improvements.

### 3. Secondary Endpoints

The secondary endpoints in Study 326 were intended to support the primary endpoints, and generally reflect the same assessment domains as their primary endpoint counterparts. As your Petition points out, neither secondary endpoint achieved statistical significance (Petition at 4). Presumably, you make this point to underscore your arguments that Aricept 23 has not demonstrated effectiveness for its indicated use. However, results for MMSE and ADCS-ADL scores in Study 326 do not alter FDA's conclusion regarding the efficacy of Aricept 23.

The MMSE, like the SIB, measures cognitive functioning.<sup>35</sup> Given the statistical strength of the SIB score improvement between the two patient study groups, one might expect to see a corresponding difference in MMSE scores. However, the MMSE is not generally used as a primary effectiveness endpoint because it is less able to detect cognitive improvement in more severely impaired patients.<sup>36</sup> Therefore, the lack of statistically significant improvements in MMSE scores for Aricept 23 does not undermine the finding on the SIB score.

The ADCS-ADL, like the CIBIC+, assesses a patient's overall functioning.<sup>37</sup> As with the CIBIC+ results, the difference in ADCS-ADL scores between Aricept 23 and Aricept 10 was not statistically significant.<sup>38</sup> Again, this lack of statistical significance does not

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<sup>34</sup> Aricept Labeling, p. 11. A lack of statistical significance for Study 326's Aricept 23 patients is not altogether surprising, given the performance of other approved dementia drugs on the CIBIC+ metric.

<sup>35</sup> See, e.g., Schmitt FA, Cragar D, Ashford W, Reisberg B, Ferris S, Mobius H-J, and Stoffler A. Measuring cognition in advanced Alzheimer's disease for clinical trials. *J Neural Transm* 2002; (Suppl) 62:135-148.

<sup>36</sup> Schmitt FA, Ashford W, Ernesto C, Saxton J, Schneider LS, Clark CM, Ferris SH, Mackell JA, Schafer K, Thal LJ. The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. *The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S51-6; Schmitt FA, Cragar D, Ashford W, Reisberg B, Ferris S, Mobius H-J, and Stoffler A. Measuring cognition in advanced Alzheimer's disease for clinical trials. *J Neural Transm* 2002; (Suppl) 62:135-148.

<sup>37</sup> Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S33-9; Reisberg B. Global measures: utility in defining and measuring treatment response in dementia. *Int Psychogeriatr* 2007;19:421-455.

<sup>38</sup> See Statistical Review, p. 22.

vitate the importance of the improvement in cognitive functioning seen in the Aricept 23 patients.

## **B. Safety**

Your Petition raises several safety-related issues pertaining to Aricept 23 (Petition at 4-11). In support of your assertion that this drug is unsafe for patient use, you discuss adverse events (both in Study 326 and in medical literature), pharmacokinetics, and the FDA pharmacology analysis relating to Aricept 23 (Petition at 4-11). For the reasons explained below, FDA finds your arguments unpersuasive.

### **1. Adverse Events (AEs) - Study 326**

You state that Aricept 23 “significantly increased [AEs]” in comparison to Aricept 10 in Study 326 (Petition at 1).<sup>39</sup> In support of your assertion, you state that 19% of Aricept 23 patients discontinued participation in Study 326 due to adverse events, as opposed to 8% of patients taking Aricept 10 (Petition at 5-6). You also cite data suggesting that nausea, vomiting, and dizziness increase in a dose-proportionate manner when comparing these events in Aricept 10 versus Aricept 23 patients (Petition at 7).<sup>40</sup> Although Study 326 suggests that the rates of these AEs were greater in subjects taking Aricept 23 vs. Aricept 10, these observations are insufficient to conclude that Aricept 23 is unsafe or that its risks outweigh its benefits for its approved use.

As discussed in the preceding sections, Aricept 23 provided statistically significant improvement in cognitive performance. When these gains are balanced against the increased risk of AEs described in the literature and in Study 326, FDA believes that the benefit-risk profile of Aricept 23 is an acceptable one for moderately to severely afflicted AD patients. Healthcare providers should choose the dose that is appropriate for each individual patient, taking into account the patient’s history and the risks and benefits of the drug.

#### **Vomiting**

In discussing individual AEs, you state that vomiting is “especially troubling” (Petition at 5). It is true that the incidence of vomiting overall was 9.2% in the Aricept 23 group, and only 2.5% in the Aricept 10 group.<sup>41</sup> Furthermore, as you note, 2.9% of patients in the Aricept 23 group discontinued the study due to vomiting, as compared to 0.4% of patients in the Aricept 10 group,<sup>42</sup> and the “mean duration of vomiting” was approximately 4

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<sup>39</sup> It should be noted, however, that the data from Study 326 show that a greater percentage of Aricept 10 patients than Aricept 23 patients reported at least one “serious” treatment-emergent sign or symptom (9.6% of Aricept 10 patients vs. 8.3% of Aricept 23 patients). See Medical Review, p. 48.

<sup>40</sup> Notably, however, the incidence of abdominal pain and headache did not demonstrate a typical dose-response pattern. Medical Review, p. 65. Indeed, there was actually a lower incidence of headaches reported in the Aricept 23 group than the Aricept 10 group. *Id.*

<sup>41</sup> Aricept labeling, p. 2, section 5.3.

<sup>42</sup> *Id.* The AEs causing the highest percentages of discontinuation in Aricept 23 patients were vomiting, nausea, and diarrhea, in that order. See, e.g., Medical Review, p. 51.

times as long in the Aricept 23 group (5.6 days) as in the Aricept 10 group (1.3 days)<sup>43</sup> (Petition at 6). FDA takes seriously the problems that may be associated with vomiting in AD patients (e.g., “pneumonia,<sup>44</sup> massive gastrointestinal bleeding, esophageal rupture, or death”<sup>45</sup>). When viewed in light of the potential benefits of Aricept 23, however, the risk and extent of vomiting shown for patients taking the drug does not require its withdrawal from the market.

Dose comparisons aside, the data you cited showed that, on average, vomiting on Aricept 23 lasted less than a week, occurred at the beginning of Aricept 23 treatment, and was not considered “severe.”<sup>46</sup> More than 9 out of 10 Aricept 23 patients will not experience any vomiting at all, and for those who do, the vomiting is likely to manifest in brief and transient episodes. Moreover, this side effect may disappear when the body adjusts to the higher dose of medication, and there is always the option of decreasing the dose or discontinuing therapy if the effect is not tolerated. When viewed in this light, it is reasonable to conclude that healthcare providers for patients whose conditions warrant high-dose treatment should have the option to accept these risks in return for the greater effectiveness of Aricept 23.

### **Other AEs**

Most of the AEs reported in subjects taking Aricept 23 in Study 326 were considered mild to moderate in severity. Nausea (12%) and diarrhea (8.3%), in addition to vomiting (9.2%); were the most frequently reported adverse events.<sup>47</sup> Other AEs included fatigue (2.4%), asthenia (2.1%), urinary tract infections (4.4%), fall (4.0%), contusion (2.1%), weight decrease (4.7%), anorexia (5.3%), dizziness (4.9%), headache (4.3%), somnolence (2.1%), agitation (3.9%), insomnia (3.4%), aggression (2.7%), and urinary incontinence (2.5%).<sup>48</sup> While the rates of some of these AEs were higher among Aricept 23 patients when compared to Aricept 10 patients, the incidences of agitation, aggression, falls, and urinary tract infections were roughly comparable between the two groups. The overall percentage of Aricept 23 patients reporting at least one serious AE was 8.3%, which is slightly less than the overall percentage of Aricept 10 patients reporting at least one serious AE (9.6%).<sup>49</sup>

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<sup>43</sup> Medical Review, p. 52.

<sup>44</sup> Two Aricept 23 patients in Study 326 died of aspiration pneumonia. See Medical Review, p. 50. However, both deaths were deemed unlikely to be related to donepezil. See Medical Review, pp. 59, 64.

<sup>45</sup> Medical Review, p. 60.

<sup>46</sup> Medical Review, p. 52; Aricept labeling, p. 2, section 5.3.

<sup>47</sup> See Medical Review, p. 52.

<sup>48</sup> See id.

<sup>49</sup> Id at 50. The serious AEs reported by Aricept 23 patients include: atrial fibrillation (0.4%), bradycardia (0.4%), diarrhea (0.4%), vomiting (0.3%), hypothermia (0.1%), pneumonia (0.3%), urinary tract infection (0.6%), fall (0.6%), femur fracture (0.4%), dehydration (0.3%), dizziness (0.4%), presyncope (0.3%), syncope (0.2%), aggression (0.2%), confusional state (0.1%), acute renal failure (0.3%), and aspiration pneumonia (0.3%). See id.

While FDA does not minimize the potential impact of these AEs on a patient's health or quality of life, the Agency nevertheless believes that the benefits of Aricept 23 outweigh its risks for patients with moderate or severe AD. The Agency reiterates that there are very few drugs available to treat AD, and even fewer drugs available to treat its severe stage. On the whole, Aricept 23's AE risks are acceptable when viewed in light of the cognitive improvement the drug offers. We believe physicians should have this drug available to prescribe to those patients who could benefit from, and would be likely to tolerate, a higher-dose donepezil regimen.

## 2. Adverse Events Reported in Other Studies and Publications

In addition to discussing the AEs seen in Study 326, you cite several studies and AE reports in support of your argument that Aricept 23 is unsafe (Petition at 9-11). Specifically, you cite literature reporting cases of agitation, aggression, nightmares, Pisa syndrome,<sup>50</sup> bradycardia, QT interval elongation, and urinary incontinence in donepezil patients (Petition at 9-11). FDA has reviewed the evidence supplied in your Petition, and has conducted additional reviews of its AE databases. None of the evidence that FDA has analyzed to date is sufficient to warrant withdrawal of Aricept 23.

With one exception, the English language<sup>51</sup> reports or studies you cited did not appear to compare 5 or 10 mg doses of donepezil to higher doses of donepezil, or compare a 23 mg dose with placebo. In fact, two of those reports or studies did not specify any donepezil dose at all,<sup>52</sup> and one reported a case completely devoid of donepezil use history.<sup>53</sup> Consequently, the cited reports or studies did not provide any evidence that Aricept 23 showed an increased risk of AEs over Aricept 5 or 10. Furthermore, all but three<sup>54</sup> English language reports or studies described a limited number of cases, and lacked comparison groups. These case reports thus do not allow a determination of whether

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<sup>50</sup> Pisa syndrome is "[a] condition in which there is sustained involuntary flexion of the body and head to one side and slight rotation of the trunk so the person appears to lean like the Leaning Tower of Pisa." <http://www.medterms.com/script/main/art.asp?articlekey=13792>.

<sup>51</sup> Two of the articles you cited were only available in foreign languages, and you did not provide either the original articles or their translations, as required by 21 C.F.R. 10.20(c)(1) and (c)(2). See Singer M, Romero B, Koenig E. Nightmares in patients with Alzheimer's disease caused by donepezil: therapeutic effect depends on the time of intake. *Nervenarzt* 2005;76:1127-9; Huvent-Grelle D, Roche J, Gaxatte C. Relation between Pisa syndrome and cholinesterase inhibitors in a cohort of Alzheimer's disease patients. *Presse Med* 2009;38:150-3. Therefore, FDA is unsure whether these studies evaluated the relevant doses of donepezil, and excludes them from consideration pursuant to 21 C.F.R. 10.20(c)(6).

<sup>52</sup> See Arora A, Verma A, Ashraf J. Donepezil and the leaning tower of Pisa. *J Am Ger Soc* 2008;56:73-4; Cholinesterase inhibitors and cardiac arrhythmias. *Aust Adv Drug Reactions Bull* 2004;23:19-20.

<sup>53</sup> See Fisher A, Davis M. Prolonged QT interval, syncope, and delirium with galantamine. *Ann Pharmacotherapy* 2008;42(278-283):278-83.

<sup>54</sup> These three exceptions are: Park-Wyllie LY, Mamdani M, Li P. Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study. *PLoS Medicine* 2009;3(9):el000157; Gill S, Mamdani M, Naglie G. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med* 2005;165:808-13; Donepezil: heart block and ventricular tachyarrhythmia (first report) in an elderly patient: case report. *Reactions Weekly* 2006 Sep 30;1121:10; Hernandez RK, Farwell W, Cantor MD, et al. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England Healthcare System. *J Am Geriatr Soc* 2009;57:1997-2003.

exposure to Aricept 23 increases the risk of specific AEs,<sup>55</sup> or raises these risks to an unacceptable level.

The only study you cited that both included a comparison group and considered donepezil dosing in the analyses was a cohort study using administrative and clinical data from the New England Veterans Affairs Healthcare System (Hernandez study).<sup>56</sup> The relevant analysis compared three dose categories (maximum doses of 5 mg, 10 mg, and greater than or equal to 15 mg donepezil per day) to the absence of donepezil exposure (0 mg). This study analyzed treatment-emergent bradycardia,<sup>57</sup> which is an AE described in Aricept labeling.<sup>58</sup> In the Hernandez study, *bradycardia* was defined by a subject having one or more International Classification of Disease 9<sup>th</sup> Revision - Clinical Modification (ICD-9-CM) codes for bradycardia. The Hernandez study data suggested both that donepezil exposure was associated with a higher risk of bradycardia, and that there was a dose-response relationship for this AE, with 5, 10, and 15 mg or greater having risks of bradycardia of 1.1, 1.3, and 2.1 times that in untreated patients, respectively. This trend is consistent with Study 326's data, which also suggested an increasing risk of bradycardia associated with an increasing donepezil dose. (There, 0.4% of Aricept 23 subjects had serious bradycardic events, and 0.7% of Aricept 23 subjects discontinued the study due to bradycardia.<sup>59, 60</sup>) As noted above, however, bradycardia is listed as an AE on Aricept 23's label, and it is an event that can be monitored by a patient's physician (e.g., via electrocardiographs).

FDA also conducted a search for AEs associated with Aricept 5, 10, and 23 from the Adverse Event Reporting System (AERS),<sup>61</sup> and reviewed relevant Periodic Safety Update Reports (PSURs).<sup>62</sup> The case reports described originated from both consumers

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<sup>55</sup> You cite four case reports or series involving Pisa syndrome and QT elongation, neither of which is described as an AE on the Aricept label (Petition at 9-10). One of these (by Huvent-Grelle et al.) is available only in French. See n. 51, supra. Another describes a case involving galantamine rather than donepezil. See n. 53, supra. The third fails to specify donepezil dose. See Arora A, Verma A, Ashraf J. Donepezil and the leaning tower of Pisa. *J Am Ger Soc* 2008;56:73-4. The fourth is uncontrolled, and involved a single case receiving only 5 mg of donepezil. See Takaya T, Okamoto M, Yodoi K. Torsades de Pointes with QT prolongation related to donepezil use. *J Cardiol* 2009;(54):507-11. Therefore, these reports do not support a causal relationship between Aricept 23 and either Pisa syndrome (which was not observed in sponsor studies) or QT elongation. Significantly, in Study 326, FDA determined that reports of QT interval elongation were not able to be linked with donepezil use. See Medical Review, pp. 53-54.

<sup>56</sup> Hernandez RK, Farwell W, Cantor MD, et al. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the Veterans Affairs New England Healthcare System. *J Am Geriatr Soc* 2009;57:1997-2003.

<sup>57</sup> *Bradycardia* is the term used to refer to a slow heart rate, regardless whether the slow heart rate has any clinical consequences for the patient. FDA does not know the exact criteria (e.g., in terms of beats per minute) used in either the Hernandez study or the Aricept 23 studies.

<sup>58</sup> Aricept labeling, p. 2, section 5.2.

<sup>59</sup> None of these events occurred in Aricept 10 patients. Medical Review, pp. 50-51.

<sup>60</sup> However, the results from the Hernandez study and the bradycardic events noted in Study 326 cannot be directly compared due to the way those results were calculated.

<sup>61</sup> The AERS database was queried on 9/7/11.

<sup>62</sup> The PSUR data used was from 11/26/09 through 11/25/10.

and health professionals, and a total of 57 cases were identified for Aricept 23.<sup>63</sup> Two of those cases were deaths of patients taking Aricept 23, but in neither case was there sufficient information to determine whether the deaths were related to the drug.<sup>64</sup> The other 55 cases were primarily nonserious gastrointestinal AEs that appeared to be aligned with Aricept's labeling.<sup>65</sup> These AE reports do not provide new safety data or evidence of clinical experience that show Aricept 23 is unsafe for its approved use.

In sum, FDA believes that Aricept 23's safety risks are acceptable in light of its benefits for patients with moderate to severe AD. The Agency further believes that Aricept 23's labeling adequately describes these risks, and enables healthcare providers to make informed decisions regarding treatment.

### 3. Pharmacokinetics and Pharmacology

You discuss several different aspects of Aricept 23's pharmacokinetics and FDA's clinical pharmacology reviews in your Petition (Petition at 8-9). However, many of your assertions are mere restatements of reviewer findings, and you have not provided any additional evidence on these subjects for FDA's consideration.

Your Petition notes donepezil's long half-life, and expresses concern that this is "a disadvantage" to those suffering from AEs (Petition at 8). You also articulate six factors affecting plasma drug levels, but do not state how they relate to your request that Aricept 23 be removed from the market (Petition at 8). Although you do not specifically request labeling changes related to Aricept 23's pharmacokinetics or pharmacology, we have determined that all necessary explanations of the drug's behavior *in vivo* are already included in Aricept's labeling.

With respect to PK studies, you imply that Aricept 23 has not been sufficiently characterized in the elderly (Petition at 8).<sup>66</sup> We disagree. Eisai evaluated the pharmacokinetics of Aricept 23 in Study 326, which was composed almost entirely of elderly patients. Overall, donepezil concentration data were available for 1154 study patients, each of whom had an average of 4 plasma concentration samples collected. These data were sufficient to support a population PK analysis that both (1) characterized fully the pharmacokinetics of donepezil (Aricept 10 and Aricept 23), and (2) analyzed the

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<sup>63</sup> The AERS and PSUR systems included approximately 6,000 reports identified for Aricept 5 and/or Aricept 10, potentially including duplicates. Three of the top four most frequently reported terms associated with these Aricept 5 and/or Aricept 10 reports included terms associated with gastrointestinal events (i.e., nausea, vomiting, and diarrhea).

<sup>64</sup> One death was in a patient who had been taking Aricept 23 for 3 months, at which point he experienced several AEs or health issues (including weight loss, nausea, bleeding, fever sores, cold, delusions, aggression, hostility, neuralgia, post nasal drip, inability to empty bladder, dizziness, fatigue, toothache, and atrial fibrillation), and eventually died after contracting pneumonia. The report did not include laboratory data, diagnostic findings, past and pre-existing medical conditions, or concomitant medications. The second death report had even less data, lacking such basic information as patient age, the date upon which she began taking Aricept 23, her concomitant medications, and the cause of death.

<sup>65</sup> See Aricept Labeling, section 5.3, p. 2.

<sup>66</sup> Specifically, you state, "[m]ost of the pharmacokinetic studies were conducted on healthy young adults, making it difficult to transfer results directly to elderly patients" (Petition at 8).



impact of certain covariates (age, gender, weight, CYP2D6 polymorphism, and CYP2D6 inhibitors<sup>67</sup>) on plasma concentrations of donepezil.<sup>68</sup> Thus, FDA has concluded that the sponsor provided sufficient PK information in the drug's target population, and that those studies support FDA's decision that Aricept 23 should remain on the market with its labeling unchanged.

Your Petition also mentions that FDA has required Eisai to conduct additional studies to examine the potential for neurodegeneration relating to the co-administration of donepezil and memantine (Petition at 9). It should be noted that the approval letter for Aricept 23 articulated two other risks that require additional studies: (1) the potential for adverse events due to increased exposure of the substrates of CYP2B6, CYP2C8, and CYP2C19, if donepezil is co-administered with the substrates and is an inhibitor of the three enzymes; and (2) the safety risk of increased exposure to donepezil, if donepezil is a P-glycoprotein substrate and is co-administered with P-glycoprotein inhibitors. Those trials have been completed, and FDA currently is analyzing the results. Once these reviews are complete, the Agency will take any action(s) it deems appropriate to protect patient health.

Finally, you raise the issue of Aricept 23's characterization as an IR drug, rather than a sustained-release or CR drug (Petition at 8-9). As you correctly note, FDA's reviewers determined that Aricept 23 lacks the characteristics of a CR drug (Petition at 8-9). Presumably, then, you are using the statements in Dr. Marroum's biopharmaceutics review that the Aricept 23 NDA was "deficient" and, consequently, "should never have been filed"<sup>69</sup> as an argument that the NDA was never valid in the first place,<sup>70</sup> and therefore should be withdrawn now. However, characterization of a drug's release profile does not affect the fileability of an NDA.<sup>71</sup> Aricept 23 was not approved, and is not marketed, as a CR product. The difference between Eisai's description of Aricept 23

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<sup>67</sup> In your petition, you state that one factor affecting plasma drug levels is "co-administration of any drugs that are CYP2D6 inhibitors that would prevent metabolism of donepezil" (Petition at 8). However, FDA disagrees with this statement. CYP2D6 inhibitors do not prevent or block donepezil metabolism, particularly as CYP3A4 also is involved in donepezil metabolism. See Aricept Labeling, section 7.2, p. 6; Aricept Labeling section 12.2, p.7. CYP2D6 inhibitors merely reduce donepezil metabolism. See, e.g., Aricept Labeling, section 7.2, p. 6 ("A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease. Donepezil clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with a known CYP2D6 inhibitor.").

<sup>68</sup> Clinical Pharmacology Review, p. 82, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022568Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf).

<sup>69</sup> Biopharmaceutics Review, p. 1 (Web page 93), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022568Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf).

<sup>70</sup> However, you do not specify the deficiencies or grounds upon which you believe FDA should have refused to file the NDA. See generally 21 C.F.R. 314.101.

<sup>71</sup> See 21 C.F.R. 314.101(d) and (e) (stating the bases upon which FDA "may" or "will" refuse to file a drug application, respectively).



in its NDA and FDA's understanding of the drug's release activity does not now support removal of Aricept 23 from the market.<sup>72</sup>

### **C. FDA Decision-Making**

Your Petition states that Aricept 23 should be withdrawn from the market because Aricept 23 "received negative reviews from both the FDA clinical and statistical reviewers" (Petition at 1). You note that Drs. Massie and Mani, the statistical and medical reviewers, respectively, recommended against approval (Petition at 11-12), largely because of the failure to show superiority to Aricept 10 on the CIBIC+. FDA believes, however, that the approval of the 23 mg dose of this drug for the treatment of moderate to severe AD was an appropriate decision, and that the benefits of Aricept 23 outweigh its risks for its labeled indication.

Intra-agency disagreements regarding drug approval recommendations are not uncommon. Every drug approval decision represents a balance of the benefits and risks of treatment, and findings may be inconsistent within and between studies. In the case of Aricept 23, Dr. Russell Katz, the Director of the Division of Neurology Products in the Office of New Drugs, carefully reviewed his colleagues' analyses, recognizing the safety- and efficacy-related concerns they articulated.<sup>73</sup> Dr. Katz's responsibility as the signatory authority was to assess the NDA in its entirety and determine, based on the analyses of his colleagues and his own scientific judgment, whether Aricept 23 met the statutory and regulatory requirements for drug approval; in particular, whether the drug is safe and effective and whether its benefits outweigh its risks. He concluded that "the sponsor has demonstrated that the 23 mg dose of Aricept is effective, and that there is sufficient reason to believe that it may produce an increased benefit compared to the 10 mg dose in some patients,"<sup>74</sup> with the caveat that the "labeling should make explicitly clear that this dose is associated with a significant increase in the incidence of adverse events that can have significant clinical sequelae."<sup>75</sup> Thus, after a full and complete discussion of the Aricept 23 NDA among FDA colleagues, Aricept 23 was approved as both safe and effective for its indicated use.

### **D. Warning Labels for Aricept 5 and Aricept 10**

Your second request was that FDA add an additional warning to the labeling of both Aricept 5 and Aricept 10, stating that "use of 20 milligrams per day is counter indicated" (Petition at 13). You base this request on the arguments advanced and conclusions reached in advocating for your first request—that FDA withdraw Aricept 23 from the market. However, FDA has concluded that Aricept 23 is safe and effective for its labeled indication and should not be withdrawn from the market. Therefore, FDA denies your

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<sup>72</sup> You do not provide cites to any statutory or regulatory provisions you believe Eisai violated. Aricept 23 is not labeled as a controlled-release product, and thus is not misbranded, false, or misleading with respect to its release mechanism.

<sup>73</sup> See generally Summary Review, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022568Orig1s000SumR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000SumR.pdf).

<sup>74</sup> Summary Review, p. 11.

<sup>75</sup> Summary Review, p. 10.

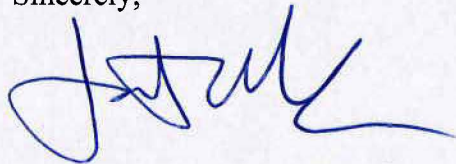
request to add a warning to Aricept 5 and/or Aricept 10 stating that “use of 20 milligrams per day is counter indicated.”

### **III. CONCLUSION**

AD is a devastating disease. It affects patients, their families, and their caregivers, and no current treatment can completely ameliorate it. Donepezil is one of only two drugs indicated for treating the severe stage of the illness, and the 23 mg dose is shown to produce added cognitive benefits over the 10 mg strength. For a disease such as AD, a physician may determine that an improvement in a patient’s cognition justifies the risk of additional side effects. FDA stands by its approval decision, and believes that physicians should have the option of prescribing Aricept 23 to those patients who could benefit from it.

Thus, after careful consideration, and, in light of the foregoing, we deny your Petition. Please be assured, however, that FDA remains committed to ensuring an appropriate balance of safety and efficacy for all approved drugs. FDA will continue to monitor Aricept 23 as required by applicable laws and regulations, and, if necessary, will take appropriate action to protect the public health.

Sincerely,

A handwritten signature in blue ink, appearing to read "Janet Woodcock", with a long horizontal flourish extending to the right.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research