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May 18, 2011

Margaret A. Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg:

Public Citizen, representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market the 23 milligram (mg) dose of Aricept (donepezil; Eisai Co., Ltd; Pfizer Inc.) because in the primary clinical trial:

1) The 23 mg dose of Aricept failed to meet the two efficacy criteria required by FDA as a condition of approval of drugs for dementia, specifically required for Aricept 23 in this case.

2) The 23 mg dose of Aricept significantly increased adverse events compared with the previously approved 10 mg dose, including increased risks for nausea, vomiting, diarrhea, anorexia, and confusion.

3) The 23 mg dose of Aricept received negative reviews from both the FDA clinical and statistical reviewers.

I. BACKGROUND

A. Current FDA-approved indications

Aricept (donepezil) was first approved November 25, 1996, for the treatment of mild to moderate Alzheimer's disease at a dose of 5 or 10 mg once a day. On October 13, 2006, Aricept was approved for severe Alzheimer's disease at a dose of 10 mg once a day, and most recently, on July 23, 2010, Aricept was approved for moderate to severe Alzheimer's disease at a dose of 23 mg per day.

B. Mechanism of action

Donepezil is an inhibitor of the enzyme, acetylcholinesterase, an enzyme that breaks down acetylcholine, thereby terminating its action. Under normal physiological conditions, this conversion is very fast (milliseconds). However, in the case of someone taking a drug that inhibits this enzyme, such as donepezil, where the enzyme deactivating acetylcholine is blocked, acetylcholine levels are maintained at high levels for much longer times.

Acetylcholine is an important neurotransmitter released from nerve endings in many organs and tissues throughout the body. Since donepezil is also distributed widely in the body, its effects are seen in many organs including the heart (slowing the rate), the skeletal muscles (causing contraction), the gastrointestinal tract (causing increased motility and tone), and the brain (where it affects behavior).

II. REQUIREMENTS FOR APPROVAL (23 mg dose of donepezil)

At a March 19, 2007, meeting between the FDA and Eisai to establish the requirements for drug approval, the FDA agreed to accept Eisai's request for submission of a single Phase 3 clinical study for the 23 mg/day dose of donepezil, assuming the following conditions were met (as recorded in the meeting notes):

> The current regulatory standard requires that the effectiveness of a treatment for Alzheimer's Disease be demonstrated on both a cognitive and a global (or functional) primary efficacy measure…Thus, [Study 326] can be considered to provide substantial evidence of effectiveness for the 23 mg/day dose…formulation of Aricept *only if that dose is demonstrated to have a statistically significant superiority over the 10 mg/day dose of the immediate-release formulation on both primary efficacy measures*, the [Severe Impairment Battery] and the [Clinician's Interview-Based Impression of Change(Plus version)].[1] [emphasis added]

This requirement for statistical significance on both co-primary endpoints was reiterated several times during this meeting.[2]

III. EFFICACY (FDA MEDICAL REVIEW)

As agreed upon by the FDA and Eisai, only one trial (Study 326) was submitted to the FDA for the approval of the 23 mg dose of donepezil for treatment of moderate to severe Alzheimer's disease.

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[1] Katz R. FDA memorandum of March 19, 2007, meeting minutes. March 28, 2007. Web page 42. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000Admincorres.pdf. Accessed April 29, 2011.

[2] Katz R. FDA memorandum of March 19, 2007, meeting minutes. March 28, 2007. Web pages 40-47. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000Admincorres.pdf. Accessed April 29, 2011.

A. Study design

Study 326 was a randomized, double-blind, active-controlled, parallel-arm study of 24 weeks duration. The primary objective was to compare two doses of donepezil: 10 mg/day (n=486) with 23 mg/day (n=981). The study was conducted in 220 sites in 23 countries. Inclusion requirements specified that subjects must have been on a daily dose of 10 mg of donepezil for at least 3 months prior to entry and have probable Alzheimer's disease (moderate to severe). Subjects were required, among other things, to be generally healthy and ambulatory and have clinical laboratory data within normal limits. If they had other disease conditions, these were to be stable. They could be on any of the following drugs if the doses of each had been stable prior to study entry: memantine (another drug approved for treatment of Alzheimer's disease), vitamin E, fish oil, ginkgo biloba, benzodiazepines, and/or a bronchodilator.

B. Co-primary endpoints of the trial[3]

The required co-primary endpoints measured the change from baseline to week 24 using the intent-to-treat population (any patient who had at least one dose). The two tests that were agreed upon by the FDA and Eisai to measure progress were the Severe Impairment Battery (SIB) and Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus).

SIB is a cognitive outcome measure with scores ranging from 0 to100 (worse to better). The SIB assesses the following cognitive domains: attention, orientation, language, memory, praxis, visuospatial perception, construction, social skills, and orientation to name.

CIBIC-Plus is a measure of how a patient is functioning with scores ranging from 1 (markedly improved) to 7 (markedly worse). The CIBIC-Plus measures the following domains of patient function: general, mental/cognitive state, behavior, and activities of daily living.

The results of Study 326 are summarized in Table 1:

Table 1. Primary endpoints: change from baseline at 24 weeks

Test	10 mg dose	23 mg dose	P value
SIB	0.4	2.6	0.0001
CIBIC-Plus	4.3	4.2	0.18

With only one of the co-primary endpoints, the change in SIB score from baseline, demonstrating a very small, but statistically significant, difference of only 2.2 (2.6 minus 0.4) on a 100-point scale, and the CIBIC test no significant difference, the FDA reviewer concluded that "The results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD)." The study failed

[3] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web pages 25 and 39-40, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

to meet its pre-specified target criteria for demonstrating the efficacy of the 23 mg dose of donepezil.[4]

Casting further doubt on the strength of even the significant SIB number, the statistical reviewers observed that "There was more missing week 24 SIB data in the 23 mg SR group than in the 10 mg IR group (24% vs. 13%) and the 23 mg dropouts also tended to dropout earlier than the 10 mg group."[5]

C. Secondary endpoints:

There were two secondary endpoints: the score on the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), which contains 45 items rated by the investigator, with information supplied by the caregiver, and the score on the Mini-Mental Status Examination (MMSE), a 30-item test for cognitive impairment. Higher scores on each instrument indicate better results. [6]

These secondary efficacy parameters were intended to support the primary efficacy analysis. Yet, according to the medical reviewer, "no statistically significant treatment difference was seen between the treatment groups on the 2 secondary efficacy measures, the ADCS-ADL and the MMSE."[7]

IV. EFFICACY (FDA STATISTICAL REVIEW)

The statistical reviewers found several problems with Study 326:

1) Primary endpoints: For one of the two required co-primary endpoints, CIBIC-Plus, the treatment difference was not statistically significant.

2) Post hoc analyses: Although some post-hoc subgroups were nominally significant, this does not meet usual standards of analysis. Furthermore, the results of these post-hoc subgroups were inconsistent and would need to be replicated.[8]

V. SAFETY (FDA MEDICAL REVIEW):

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[4] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[5] Massie TS, Jin K, Hung HM. FDA statistical review for NDA application number 022568. July 9, 2010. Web page 24. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000StatR.pdf. Accessed April 29, 2011.

[6] Mani RB. FDA medical officer review for NDA application number 022568 July 23, 2010. Web pages 24 and 26. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[7] Mani RB. FDA medical officer review for NDA application number 022568 July 23, 2010. Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[8] Massie TS, Jin K, Hung HM. FDA statistical review for NDA application number 022568. July 9, 2010. Web page 41. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000StatR.pdf. Accessed April 29, 2011.

Adverse events leading to discontinuations were higher in the 23 mg group and included nausea, vomiting, and anorexia. Vomiting was especially troubling, with a rate of 9.2% (23 mg dose) vs. 2.5% (10 mg dose) since, according to the FDA medical reviewer, "...vomiting can lead to even greater morbidity in patients with Alzheimer's Disease, that includes pneumonia, massive gastrointestinal bleeding, esophageal rupture, or death. Thus, in addition to lacking any evidence of a clinically meaningful benefit, at least in comparison with the 10 mg QD [once a day] dose of donepezil, the use of a 23 mg QD dose (i.e., an escalation in dose from 10 mg QD) is also associated with a significant risk to patient safety."[9]

Table 2. Patient disposition in study 326[10,11]

	10 mg	**23 mg**
Randomized	486	981
Safety population	471	963
Intention to treat	462	909
Completed	399 (82%)	685 (70%)
Discontinued	87 (18%)	296 (30%)
Discontinued due to adverse events	39 (8%)	182 (19%)

It can be seen in Table 2 that a much higher percentage of subjects discontinued the 23 mg dose than discontinued the 10 mg dose (30% vs. 18%) and that the percentage of subjects who discontinued due to an adverse event was more than twice as high in the 23 mg dose group than in the 10 mg dose group (19% vs. 8%).

Table 3 shows the types and percentages of adverse effects that led patients to discontinue the study.

Table 3. Discontinuations due to adverse effects[12]

Adverse event	**10 mg dose**	**23 mg dose**
Total emerging AEs	7.9%	19%
Cardiac		
Bradycardia	0.0%	0.7%
QT elongation	0.0%	0.4%

[9] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 6-7 and 61-62. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[10] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web pages 33-34; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[11] Massie TS, Jin K, Hung HM. FDA statistical review for NDA application number 022568. July 9, 2010. Web page 15. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000StatR.pdf. Accessed April 29, 2011.

[12] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 52. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

Gastrointestinal		
Nausea	0.4%	1.7%
Vomiting	0.4%	2.9%
Diarrhea	0.4%	1.7%
Fatigue	0.8%	2.4%
Metabolism		
Anorexia	0.2%	0.3%
Nervous system		
Dizziness	0.0%	1.1%
Headache	0.0%	0.4%
Somnolence	0.0%	0.6%
Syncope	0.4%	0.2%
Psychiatric		
Aggression	0.4%	0.5%
Agitation	0.2%	0.8%
Confusional state	0.0%	0.7%

It can be seen from Table 3 that more than twice the percent of patients in the 23 mg dose group discontinued because of adverse effects compared to the 10 mg dose group. Adverse events leading to discontinuation that were substantially higher in the 23 mg dose group included slow pulse rate, nausea, vomiting, diarrhea, fatigue, dizziness, agitation and confusion.

Discontinuations due to vomiting occurred at a seven times higher rate in the 23 mg dose group than in the 10 mg dose group: 2.9% vs. 0.4%. Furthermore, the mean duration of vomiting was much longer in the 23 mg dose group: 5.6 days (23 mg) vs. 1.3 days (10 mg) (most cases were deemed "moderate" in severity, although "moderate" was not defined).[13]

Table 4 demonstrates the increasing frequency of adverse events as the dose is increased, consistent for all eight of the most commonly occurring adverse events.

Table 4. Most common adverse events of donepezil use (all patients, not just dropouts)[14]

Adverse event	10 mg dose	23 mg dose
Nausea	3.4%	12%
Vomiting	2.5%	9.2%
Diarrhea	5.3%	8.3%
Fatigue	0.8%	2.4%
Confusion	0.2%	2.1%
Weight decrease	2.5%	4.7%

[13] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 53. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[14] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 53. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

Anorexia	1.7%	5.3%
Urinary incontinence	1.3%	2.5%

Table 5 shows the results of a study specifically designed to examine the effects of increasing doses of donepezil on frequency of adverse events; all events except headache were higher at 23 mg.

Table 5. Dose-response study of donepezil[15]

Adverse event	10 mg IR (n=26)*	14 mg SR (n=23)*	23 mg SR (n=33)*
Nausea	30%	52%	71%
Vomiting	26%	30%	65%
Dizziness	30%	26%	32%
Abdominal pain	3.7%	0%	18%
Headache	15%	0%	8.8%

**Exposure: 10 mg (one week), 14 mg (two weeks), 23 mg (two weeks)*

VI. DEATHS

There were 13 deaths during and up to 30 days post dose; eight at 23 mg (0.8%) and five at 10 mg (1.1%).

Although all were listed as "not related" to drug, two at 23 mg were due to aspiration pneumonia, something about which the medical reviewer had warned.[16] Two deaths at 10 mg/day were due to hypothermia due to patients apparently being exposed to the outdoors without proper clothing and should clearly not be considered drug related.

Table 6. Deaths in Study 326 (taken from the NDA review)

Patient Number	Treatment Group	Day of Death (Study Day)	Cause of Death (Preferred Term)	Related to Treatment[b]
60181017	SR 23 mg		cardiorespiratory arrest (cardio-respiratory arrest)	Not related
60491003	SR 23 mg		drowning (drowning)	Not related
70271017	SR 23 mg		AE pneumonia (pneumonia aspiration)	Not related
70351010	SR 23 mg		internal bleeding from digestive tract due to gastric ulcer (gastric ulcer hemorrhage)	Not related
70001035	SR 23 mg		cardiovascular disease (cardiovascular disorder)	Not related
71071013	SR 23 mg		bilateral pneumonia (pneumonia aspiration)	Not related
71091002	SR 23 mg		sequelae of stroke (cerebrovascular accident)	Not related
71291012[c]	SR 23 mg		not provided (cardiopulmonary failure)	Not related
60021020	IR 10 mg		septic shock (septic shock)	Not related
60211007	IR 10 mg		natural causes (ischemic heart disease) (myocardial ischemia)	Not related
61011005	IR 10 mg		due to progression of Alzheimer's disease, patient ran away and died of heart failure due to hypothermia (hypothermia)	Not related
70141008	IR 10 mg		myocardial infarction (myocardial infarction)	Not related
70351011	IR 10 mg		exposure to excessive natural cold (hypothermia)	Not related

a: Patients who died prior to receiving double-blind study medication are not included in this table.
b: Investigator's assessment.
c: Patient 71291012 withdrew consent and discontinued from the study on 30 January 2009. The patient died during the 30-day follow-up period; therefore, study day of death was not applicable.
Abbreviations: IR = immediate release; SR = sustained release; N/A = not applicable.

[15] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 66. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

[16] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 50. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed April 29, 2011.

VII. FDA CLINICAL PHARMACOLOGY REVIEW

Donepezil has a very long half-life (70 hours or about 3 days), which means that it takes more than two weeks for plasma donepezil to reach a steady state level. It also means that it takes about two weeks to clear the drug from the body. This is a disadvantage if there is an adverse event, since stopping the drug does not lead immediately to cessation of the adverse event.[17]

At least six factors can affect plasma drug levels: duration of use (the concentration in plasma increases four- to five-fold after multiple doses)[18]; age (drug levels are higher in the elderly); body weight (concentration increases as body weight increases); gender (females have higher concentrations than males); the form of the drug-metabolizing enzyme CYP2D6 that an individual has (some forms metabolizes the drug faster, lowering drug levels); and co-administration of any drugs that are CYP2D6 inhibitors that would prevent metabolism of donepezil.[19]

Most of the pharmacokinetic studies were conducted on healthy young adults, making it somewhat difficult to transfer results directly to elderly patients. Further complicating the picture is that donepezil is both metabolized by and inhibits the drug-metabolizing enzymes CYP2D6 and 3A4.[20]

Drug formulation: After dose normalization, the pharmacokinetics of the 23 mg sustained-release (SR) dose were the same as the 10 mg immediate-release (IR) dose (AUC, Cmax, Cmin), and in fact, the drug label makes no claim that 23 mg is a SR formulation.[21] The medical reviewer stated that "it was determined by the Agency that the proposed new formulation did not have the characteristics of an extended-release tablet contrary to statements made in the original submission under this application."[22]

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[17] Yang X, Wang Y, Men Y, et al. FDA Clinical pharmacology review for NDA application number 022569. July 21, 2010/August 4, 2010. Web page 6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf. Accessed May 2, 2011.

[18] Yang X, Wang Y, Men Y, et al. FDA Clinical pharmacology review for NDA application number 022569. July 21, 2010/August 4, 2010. Web page 16. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf. Accessed May 2, 2011.

[19] Yang X, Wang Y, Men Y, et al. FDA Clinical pharmacology review for NDA application number 022569. July 21, 2010/August 4, 2010. Web page 7. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf. Accessed May 2, 2011.

[20] Yang X, Wang Y, Men Y, et al. FDA Clinical pharmacology review for NDA application number 022569. July 21, 2010/August 4, 2010. Web page 20. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf.

[21] Eisai Inc. Aricept drug label. Revised November 2010. http://aricept.com/pdf/AriceptComboFullPIFebruary2011.pdf. Accessed May 2, 2011.

[22] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed May 2. 2011.

The team leader of the biopharmaceutic review group was even more emphatic, stating that "This NDA is deficient in that it did not conduct the necessary studies required by the CFR [Code of Federal Regulations] to establish the controlled release nature of the formulation *and should have never been filed.*"[23] [emphasis added]

VIII. FDA PHARMACOLOGY REVIEW

No nonclinical studies were submitted to the NDA for the 23 mg dose. However, the reviewer pointed out a literature source that demonstrated that donepezil can "potentiate the neurodegeneration induced by memantine in rat brain"; therefore, the sponsor is being asked to conduct a post-marketing study in rats to further examine this issue.[24] This is important, as many patients take both drugs. For example, in this study, 35-36% of all groups were also using memantine.[25]

IX. MEDICAL LITERATURE REVIEW OF ADVERSE EVENTS (Acetylcholinesterase inhibitors — primarily donepezil): Literature reports

A. Neuropsychiatric problems

These include cases of agitation,[26] aggression,[27] nightmares,[28,29] and Pisa syndrome.[30,31]

B. Cardiovascular problems

Two large studies looked at bradycardia in dementia patients taking cholinesterase inhibitors. One study, using Canadian health care records of more than 1.4 million adults

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[23] Patrick Marroum, Team Leader FDA Biopharmaceutics review of NDA application number 022569. April 2, 2010. Web page 93. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000ClinPharmR.pdf.

[24] Hawver DB, Freed LM. FDA pharmacology review for NDA application number 022568. July 2, 2010/July 7, 2010. Web page 8. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000PharmR.pdf. Accessed May 2, 2011.

[25] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 37. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed May 2, 2011.

[26] Hemingway-Eltomey JM, Lerner AJ. Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. Am J Psy. 1999;156:1470.

[27] Bianchetti A, Trabucchi M. Aggressive behavior associated with donepezil treatment: a case report. Int J Ger Psy. 2003;18:657-658.

[28] Ross JS, Shua-Haim JR. Aricept-induced nightmares in Alzheimer's disease: 2 case reports. J Am Geriatrics Soc. 1998;46:119-120.

[29] Singer M, Romero B, Koenig E. et al. Nightmares in patients with Alzheimer's disease caused by donepezil. Therapeutic effect depends on the time of intake. Nervenarzt. 2005;76:1127-1129.

[30] Arora A, Verma A, Ashraf J, et al. Donepezil and the leaning tower of Pisa. J Am Ger Soc. 2008;56:73-74.

[31] Huvent-Grelle D, Roche J, Gaxatte C. et al. Relation between pisa syndrome and choline esterase inhibitors in a cohort of Alzheimer's disease patients. Presse Medicale. 2009; 38:150-153.

(67 years old or older), found a doubling of the rate of hospitalization for bradycardia in patients taking cholinesterase inhibitors compared to a matched control group.[32]

A study of 11,328 dementia patients in the Veterans Affairs New England Healthcare System found a 40% increase in bradycardia in patients with dementia taking cholinesterase inhibitors (90% on donepezil). There was an apparent dose dependency with patients taking donepezil doses of 15 mg per day or higher having a two-fold increase in bradycardia (slowed pulse) compared to untreated dementia patients. In addition, "It was found that patients with bradycardia were more likely to fall (adjusted HR = 2.6)...and to experience syncope (adjusted HR = 3.7)." In addition, "Patients with bradycardia were also more likely to need a pacemaker implant (0.73% vs. 0.17%)."[33] Although donepezil at doses of 15 and 20 mg/day are not FDA approved, 10% of these Alzheimer's disease patients were taking those higher doses.

Adverse reactions tabulated in Australia produced warnings about cardiac arrhythmias in patients prescribed cholinesterase inhibitors, including bradycardia, AV (heart) block, syncope, and myocardial infarction/cardiac arrest. Most cases were in patients taking donepezil. "Many patients were hospitalized and in 4 cases a pacemaker was required. Four elderly patients died from suspected myocardial infarction." [34] The article warned of interactions expected from concomitant prescribing of beta-blockers or calcium channel blockers, drugs likely to be given to elderly patients.

While, overall, the QT elongation was found to be uninterpretable in this trial, there has been a report of a case of QT elongation that resolved when donepezil was withdrawn.[35] Galantamine (another acetylcholinesterase inhibitor) also prolonged the QT interval, which resolved with withdrawal of drug (galantamine also induced syncope, delirium, vomiting, and diarrhea).[36]

An analysis by the above authors of the Australian Adverse Drug Reactions Advisory Committee database found that all three marketed acetylcholinesterase inhibitors (galantamine, rivastigmine, and donepezil) were associated with delirium/confusion/agitation, syncope, bradycardia, other arrhythmias, and hypotension. [37]

An editorial comment appended to a report of heart block and ventricular tachyarrhythmia in a patient on donepezil noted that "The [World Health Organization] Adverse Reactions

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[32] Park-Wyllie LY, Mamdani MM, Li P, et al. Cholinesterase inhibitors and hospitalization for bradycardia: a population –based study. PLoS Medicine 2009;6(9):e1000157. Doi:10.1371/journal.pmed.1000157.

[33] 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.

[34] Cholinesterase inhibitors and cardiac arrhythmias. Aust Adv Drug Reactions Bull. 2004;23:19-20.

[35] Takaya T, Okamoto M, Yodoi K, et al. Torsades de Pointes with QT prolongation related to donepezil use. J Cardiol 2009;54:507-511.

[36] Fisher AA, Davis MW. Prolonged QT interval, syncope, and delirium with galantamine. Ann Pharmacotherapy 2008;42:278-283.

[37] Fisher AA, Davis MW. Prolonged QT interval, syncope, and delirium with galantamine. Ann Pharmacotherapy 2008;42:278-283.

database contained 36 reports of heart block, 65 reports of atrioventricular block and eight reports of ventricular tachycardia associated with donepezil."[38]

C. Urological problems

Seven published case reports included two men and five women who developed urinary incontinence during donepezil therapy for Alzheimer's disease, representing 7% of total Alzheimer's disease cases at Hyogo Institute for Aging Brain and Cognitive Disorders. Incontinence developed in six of the seven when the dose was increased. "These findings strongly suggest a causal dose-dependent relation between donepezil use and urinary incontinence."[39]

Another study in 44,884 older Canadian adults with dementia concluded that the "Use of cholinesterase inhibitors is associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence" and "may represent a clinically important prescribing cascade."[40] That is, cholinesterase inhibitors were responsible for an adverse event that was then treated with a second drug, presumably because health care providers were not aware of the connection.

D. Medical reviewer's comments and conclusions

"It is a long-established requirement of this Agency that the efficacy of a drug intended for the treatment of Alzheimer's Disease should be demonstrated on both a cognitive instrument and on a global or functional measure: on a cognitive measure, because the core symptoms of Alzheimer's Disease are cognitive; and on a global or functional measure to confirm that the effect on the cognitive measure is clinically meaningful."[41]

The medical reviewer continued, "The results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD)."[42] As a result, the reviewer concluded: "*I recommend that this application*, which seeks the approval of Aricept in a new dose strength of 23 mg administered once daily, for the treatment of moderate to severe dementia of the Alzheimer's type *not be approved.*"[43] [emphasis added]

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[38] http://adisonline.com/reactions/Fulltext/2006/11210/Donepezil__Heart_block_and_ventricular.29.aspx.
[39] Hashimoto M, Imamura T, Tanimukai S, et al. Urinary incontinence: an unrecognised adverse effect with donepezil. Lancet. 2000;356:568.
[40] Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005;165:808-813.
[41] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 60. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed May 2, 2011.
[42] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed May 2, 2011.
[43] Mani RB. FDA medical officer review for NDA application number 022568. July 23, 2010. Web page 3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000MedR.pdf. Accessed May 2, 2011.

E. FDA statistical reviewers' comments

This application rests on a single study of which one of the required co-primary endpoints was not significant (p=0.179). "Unless there is some compelling prior reason to believe that there is a dose response between 10 mg IR (immediate release) and 23 mg SR (suspended release), the data from this trial does not seem to provide enough support for the efficacy of the 23 mg SR formulation."[44]

F. FDA summary review

Dr. Russell Katz, the Division Director of Neurology Products, made the decision to approve the 23 mg dose of donepezil over the objections of both the medical and statistical reviewers: "I recognize that Drs. Mani [Medical Reviewer] and Massie [Statistical Reviewer] have expressed reservations" but "I disagree."

This conclusion was in spite of Dr. Katz's recognizing that "Not only was there no statistical significance between the treatments on the primary measure of overall functioning, but there was a clear lack of significance on another accepted measure, the ADCS-ADL [a secondary endpoint]."

Dr. Katz went on to tabulate three problems with approving the 23 mg dose:

1) "There is a clear increase in the incidence of adverse events on the 23 mg dose compared to the 10 mg dose";

2) "These are not trivial events in these patients; these could lead to significant morbidities and even increased mortality";

3) These events "are of particular concern, given that these patients had all been receiving treatment with 10 mg once a day for at least three months. That is, even though patients had been tolerating (more or less) a dose of 10 mg for three months, the increase to 23 mg was clearly accompanied by a significant increase in the incidence of these events."

Dr. Katz posed the question: "Does the absence of a demonstration of any superiority of the 23 mg dose to the 10 mg dose on measures of overall functioning, coupled with the increased incidence of potentially significant adverse events, argue against the approval of this product?" His answer, in spite of all this, was "The 23 mg dose is clearly superior to the 10 mg dose on the cognitive measure [SIB]. In my view, this strongly argues for a conclusion that the 23 mg dose is very likely to also have an effect on overall functioning [CIBIC-Plus], despite this not having been demonstrated directly in this study." Thus, he approved the 23 mg dose of donepezil.

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[44] Massie TS, Jin K, Hung HM. FDA statistical review for NDA application number 022568. July 9, 2010. Web page 6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000StatR.pdf. Accessed May 2, 2011.

X. PUBLIC CITIZEN SPECIFIC RECOMMENDATIONS

It appears that in order to keep one form of donepezil available under patent protection, Eisai developed the higher 23 mg dose.[45] The division director had his own reasons for approving donepezil. Public Citizen finds the arguments of the division director completely unacceptable and concurs with the conclusions of both the FDA medical and statistical reviewers that the 23 mg dose of donepezil is ineffective. In addition, the data show that 23 mg is clearly more toxic than the 10 mg dosage strength. Combined with its lack of pre-specified efficacy, this leads to only one conclusion: the 23 mg dose should be immediately withdrawn from the market. We further ask the FDA to require an addition to the labeling of all other dosage forms of Aricept and generic donepezil (5 mg and 10 mg), a warning stating that the "use of 20 milligrams per day is counter indicated" because the toxicity of that total daily dose will be quite similar to that of Aricept 23.

XI. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

XII. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Elizabeth Barbehenn

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[45] Eisai builds defenses against generic Aricept. July 26, 2010. http://www.fiercepharma.com/story/eisai-builds-defenses-against-generic-aricept/2010-07-26.