IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PUBLIC CITIZEN, INC.,
1600 20th Street NW
Washington, DC 20009
(202) 588-1000

Plaintiff,

v.

C.A. No. _____

FOOD AND DRUG ADMINISTRATION,
5600 Fishers Lane
Rockville, MD 20854
(301) 827-2410

Defendant.

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. Plaintiff Public Citizen brings this action pursuant to the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and the Administrative Procedure Act (APA), 5 U.S.C. §§ 702 and 706, to compel the United States Food and Drug Administration (FDA) to act on Public Citizen's petition requesting that the FDA (1) withdraw from the market Aricept (donepezil hydrochloride) 23 mg tablets; and (2) add a label to the lower dosage forms of Aricept and generic donepezil (5 mg and 10 mg tablets) warning of the increased toxicity associated with higher doses. On May 18, 2011, pursuant to 21 C.F.R. § 10.30, Public Citizen petitioned the FDA to withdraw Aricept 23 mg tablets and add a warning label to the lower dose forms of the drug, citing the FDA's medical and statistical reviewers' conclusions that the 23 mg dose has no greater efficacy than the lower doses but has more severe—and potentially life-

threatening—side effects. Although more than fifteen months have passed since Public Citizen filed its petition, the FDA has neither granted nor denied the petition, and has taken no action to remove Aricept 23 mg tablets from the market or to add warning labels to the lower dose forms of the drug. Therefore, to protect public safety and prevent needless death and injury, Public Citizen seeks a declaration that the FDA has acted unlawfully by withholding action on Public Citizen's petition and an order requiring the FDA to act thereon.

PARTIES

2. Plaintiff Public Citizen is a non-profit, public interest organization headquartered in Washington, D.C., with 300,000 members and supporters nationwide. Since its founding in 1971, Public Citizen has worked before Congress, regulatory agencies, and in the courts to advance the interests of its members on a wide range of consumer protection issues. In particular, Public Citizen's Health Research Group (HRG) promotes research-based, system-wide changes in health care policy and provides oversight concerning drugs, medical devices, doctors, hospitals, and occupational health. HRG works to ban or relabel unsafe or ineffective drugs and publishes "Worst Pills, Best Pills News," a consumer guide to avoiding drug-induced death or illness. "Worst Pills, Best Pills News" has about 190,000 subscribers. Public Citizen and its members have been, and continue to be, injured by the FDA's failure to act on Public Citizen's petition and its failure to withdraw Aricept 23 mg tablets from the market and to add warning labels to the lower dose forms of the drug. As long as the 23 mg dose of Aricept remains on the market, Public Citizen's members are at risk of suffering adverse effects of this drug, including death.

3. The Department of Health and Human Services (HHS) is an agency of the federal government, and the FDA is an agency within HHS. The FDA is responsible for administration of the FDCA. In particular, the FDA is responsible for approving new drugs for marketing and for withdrawing approval of unsafe drugs, s*ee* 21 U.S.C. § 355(e), and for regulating the content and format of prescription drug labeling, *see* 21 C.F.R. § 201. As set forth in more detail below, the FDA has violated the law by failing to act on Public Citizen's petition seeking the withdrawal of marketing approval of Aricept 23 mg tablets and adequate labeling of the lower dose forms of the drug.

JURISDICTION

4. This Court has jurisdiction pursuant to 28 U.S.C. § 1331.

FACTS

5. Aricept (donepezil) is an acetylcholinesterase inhibitor used to treat Alzheimer's disease. Aricept is a drug within the meaning of the FDCA, 21 U.S.C. § 321(g)(1), and a new drug within the meaning of 21 U.S.C. § 321(p).

6. The FDCA prohibits the introduction into interstate commerce of any new drug without FDA approval. 21 U.S.C. § 355.

7. The FDCA requires the FDA to withdraw approval of unsafe drugs. 21 U.S.C. § 355(e).

8. The FDCA prohibits the introduction into interstate commerce of any drug that is misbranded. 28 U.S.C. § 331. A drug is misbranded if its labeling does not contain adequate warnings. 28 U.S.C. § 352(f).

9. Aricept is manufactured by Eisai Co., Ltd., and marketed by Pfizer, Inc. In 1996, the FDA approved Aricept as a treatment for Alzheimer's disease at a dose of 5 or 10 mg

once a day. With the patent on the 5 and 10 mg tablets set to expire in November 2010, Eisai sought approval for a 23 mg version of Aricept that would extend the patent for three more years.

10. On March 19, 2007, the FDA met with Eisai to establish the requirements for approval of the 23 mg per day dose of donepezil. The FDA agreed to Eisai's request for submission of a single efficacy study. The FDA has long-required that the efficacy of a drug intended for the treatment of Alzheimer's disease 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. Thus, the FDA informed Eisai that the proposed 23 mg formulation of donepezil would be considered effective and would be approved only if it was shown to have statistically significant superiority over the 10 mg dose on two primary efficacy measures: the Severe Impairment Battery (SIB) and the Clinician's Interview Based Impression of Change-Plus (CIBIC+). The secondary efficacy measures for the study were the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) and the Mini-Mental Status Examination (MMSE).

11. Eisai submitted the results of the study to the FDA on September 24, 2009. The study showed a small but statistically significant difference on one of the co-primary endpoints, the SIB, but no statistically significant difference in scores on the other co-primary endpoint, the CBIC+. Thus, the results of the study failed to satisfy the FDA's criteria for demonstrating the efficacy of the higher dose of donepezil. Further, the study

revealed no statistically significant treatment difference on the two secondary efficacy measures, the ADCS-ADL and the MMSE.

12. Although the study failed to show that the 23 mg dose has any clinically meaningful benefit, the study demonstrated that, in comparison with the 10 mg dose, the use of a 23 mg dose of donepezil is associated with a significant increase in risk to patient safety. Study subjects taking the 23 mg dose had a higher incidence of all adverse events. In particular, the use of the 23 mg dose was associated with a much higher incidence of vomiting, which, in patients with Alzheimer's disease, can lead to pneumonia, massive gastrointestinal bleeding, esophageal rupture, or death.

13. The results of the study were reviewed by FDA staff. The FDA's medical reviewer, Ranjit B. Mani, M.D., concluded that Eisai had failed to provide substantial evidence of the efficacy or safety of the 23 mg dose of Aricept. Thus, Dr. Mani recommended against approval of the application to market a 23 mg dose of Aricept, finding that "[t]he results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD)." Similarly, the FDA's statistical reviewers concluded that the study did not demonstrate the efficacy of the 23 mg formulation.

14. Despite the study's failure to demonstrate the efficacy of the 23 mg dose on the pre-specified criteria, and despite the FDA staff's recommendation that approval be denied, the Director of FDA's Division of Neurology Products, Russell G. Katz, M.D., decided that the FDA should approve Eisai's application to market a 23 mg dose of Aricept. Dr. Katz acknowledged that the study failed to demonstrate any superiority of the 23 mg dose over the 10 mg dose on measures of overall functioning, and that the

higher dose is associated with a significant increase in the incidence of adverse events, including those that could cause death.

15. On July 23, 2010, the FDA approved Eisai's application to market a 23 mg dose of Aricept, thereby extending Eisai's patent protection for an additional three years.

16. On May 18, 2011, pursuant to 21 C.F.R. § 10.30, Public Citizen filed a petition with the FDA urging the FDA immediately to remove from the market the 23 mg dose of Aricept and to add to the labeling of the lower dose forms of Aricept and generic donepezil a warning that the use of higher doses is counter indicated because of the increased risk of adverse events. Public Citizen's petition relied entirely on the information that was before FDA when it made its decision to approve the 23 mg dose of Aricept. Public Citizen was joined by co-petitioner Thomas E. Finucane, M.D. Dr. Finucane is Professor of Medicine in the Division of Gerontology and Geriatric Medicine at the Johns Hopkins University School of Medicine and Staff Physician at the Johns Hopkins Bayview Medical Center. Dr. Finucane is a member of the John Hopkins Berman Institute of Bioethics and of the Editorial Board of the *Journal of the American Geriatrics Society*.

17. On June 7, 2011, the FDA acknowledged receipt of Public Citizen's petition and assigned it docket number FDA-2011-P-0455-0001/CP. By letter dated December 1, 2011, the FDA indicated that it had not yet reached a decision because the petition "raises significant issues requiring extensive review and analysis by Agency officials."

18. Public Citizen's petition provides sufficient grounds for the FDA to begin the process of withdrawing the 23 mg dose of Aricept from the market pursuant to 21 U.S.C.

§ 355(e), and to order enhanced labeling of the lower dose forms of the drug pursuant to 21 C.F.R. § 201.57(c)(1).

19. Public Citizen is entitled to a decision on its citizen petition, *see* 21 C.F.R. § 10.30(e)(2). To date, the FDA has not issued a decision on Public Citizen's petition.

20. The considerable danger to public health caused by the FDA's failure to withdraw the 23 mg dose of Aricept from the market and to add a warning to the lower dose forms of the drug counsels in favor of expeditious action on Public Citizen's petition. The pace of the FDA's decisional process is lagging unreasonably in light of the nature and extent of the public health interests at stake.

CLAIMS FOR RELIEF

21. The FDA's failure to act on Public Citizen's petition constitutes agency action unlawfully withheld or unreasonably delayed and violates the Administrative Procedure Act, 5 U.S.C. § 706(1).

22. The FDA's failure to act on Public Citizen's petition is not in accordance with law and violates the Administrative Procedure Act, 5 U.S.C. § 706(2)(A).

WHEREFORE, Plaintiff requests that this Court

A. Declare unlawful the FDA's failure to act on Public Citizen's petition;

B. Order the FDA to issue a decision on Public Citizen's petition within 30 days of declaring the FDA's failure to act unlawful;

C. Award Public Citizen its reasonable costs and attorney's fees under 28 U.S.C. § 2412; and

D. Grant all other appropriate relief.

Respectfully submitted,

/s/ Michael T. Kirkpatrick

Michael T. Kirkpatrick (D.C. Bar No. 486293)
Adina H. Rosenbaum (D.C. Bar No. 490928)
Public Citizen Litigation Group
1600 20th Street NW
Washington, DC 20009
202-588-1000
mkirkpatrick@citizen.org

Attorneys for Plaintiff Public Citizen

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