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Joan Claybrook, President

September 3, 2003

Mark B. McClellan, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Dear Commissioner McClellan:

Public Citizen, a nationwide consumer organization with a membership of more than 125,000, wishes to supplement its March 19, 2002 petition[1] (docket number 02P-0120) which called for the banning of the dangerous prescription diet drug Meridia (sibutramine, Knoll Pharmaceuticals/Abbott) due to the rising number of cardiovascular events associated with the drug. In that petition, we cited 19 deaths from cardiovascular disease that had been reported to the Food and Drug Administration (FDA) from the time of sibutramine's launch in February 1998 through the end of September 2001. Ten of the 19 cardiac deaths were in people 50 or younger, including three women under the age of 30. We have not as yet received a decision on our petition from the agency.

Since then, from reviewing subsequent FDA adverse event data, we have become aware of an additional 30 cardiovascular deaths in people using Meridia, for a total of 49 cardiovascular deaths. Twenty-seven of the 49 (68%) were in people less than 50 years old. There is no dispute that Meridia commonly causes large, sustained increases in blood pressure, a major risk factor for heart attacks and cardiac arrest, the causes of death in most patients who died after using the drug. In the clinical trials, compared to patients getting a placebo, an excess of 10% of Meridia users had a sustained increase in diastolic blood pressure of 10 mm Hg or more and 4% had a sustained increase in systolic pressure of 15 mm Hg or more at the commonly used 15 milligram dosage.[2]

Our new analysis of cardiovascular adverse events in the FDA database covers the 18-month period subsequent to our petition, i.e., from October 1, 2001 through March 31, 2003. We have also added an analysis of an adverse event not discussed in our original petition, fetal toxicity, and for that we cover the

[1] http://www.citizen.org/publications/release.cfm?ID=7160
[2] Current FDA-approved labeling for Meridia, in effect since May, 2002. (http://www.rxabbott.com/pdf/meridia.pdf accessed 8/30/03)

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entire period for which we have information (February 1998 through March 2003).

This new analysis utilized the same search criteria as was used previously: we searched on the drug names of sibutramine, Meridia, or Reductil and required that these be listed as the Primary Suspect in the adverse reaction. We have found 30 more cardiovascular deaths reported in the latest 18-month period for a total (as of the end of March 2003) of at least 49 cardiovascular deaths where sibutramine was felt to be the primary suspect as cause of death. These deaths were due mainly to myocardial infarctions or cardiac arrests, including the case of a cardiac arrest in a 28-year-old woman. The new and worrisome category of adverse events relating to adverse effects on the fetus includes spontaneous abortions, stillbirths, and congenital malformations, including those of the heart and central nervous system. As is discussed later, some of these birth defects are consistent with those seen in animal studies with the drug.

Adverse Effects of Sibutramine on the Cardiovascular System

Cardiovascular adverse events, especially increases in blood pressure and pulse rate, were seen during the pre-approval controlled clinical trials and were such a source of worry that the Medical Officer,[3] the Team Leader,[4] as well as the Advisory Committee[5] assembled to review sibutramine all recommended *against* approval. They argued that the benefits did not outweigh the risks, and they have been, unfortunately, proved correct.

In our March 2002 petition, we analyzed the FDA reviews and the advisory committee transcript and concluded that sibutramine was not safe and should be banned. At that time, over the first 44 months of marketing, there were 19 cardiovascular deaths where sibutramine was the drug listed as the primary suspect. In our new analysis of the subsequent 18 months, there were an additional 30 cardiovascular deaths (Appendix Table 1). The addition of these 30 cardiovascular deaths in just 18 additional months compared to 19 in the first 44 months represents a significantly increased rate of reports to the FDA, especially noteworthy since the reporting of adverse reactions is usually higher during the first two or three years after marketing, whereas this latter 18-month period comes in the fourth and fifth years of marketing. Of the 25 deaths (out of 30) where ages were provided, 17 (68%) were in their 20s, 30s, or 40s. These are ages where such deaths are otherwise rare. Since adverse events are underreported, the number that have actually occurred in clinical practice is much higher than reflected in the FDA data.

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[3] http://www.fda.gov/cder/foi/nda/index97.htm.
[4] Ibid.
[5] Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee, September 26, 1996.

In addition to the 30 cardiovascular deaths (since our petition of March 2002) there were at least 126 serious cardiovascular adverse events, 63 of which (50%) led to hospitalization (Appendix Table 2). These adverse events included increased blood pressure, arrhythmias, cardiac arrests, cardiac failures, and myocardial infarctions. Forty-six (37%) reports listed some form of arrhythmia.

When the 63 new reports of hospitalizations are added to the 61 reports of cardiovascular adverse events requiring hospitalization that occurred during the period covered in our original petition, there are (as of March 31, 2003) a total of 124 serious cardiovascular adverse events requiring hospitalization. These 124 hospitalizations are in addition to the 49 cardiovascular adverse events that resulted in death.

Adverse Effects of Sibutramine on the Fetus

ADVERSE EFFECTS SEEN IN TOXICOLOGY STUDIES

The FDA pharmacology reviewer reported cardiac anomalies in pups of treated rats and rabbits. In one rabbit study, there was stenosis or atresia of the pulmonary trunk or valve (narrowing or deformation of a particular cardiac valve).[6] A second rabbit study showed "a significant increase in the incidence of visceral and skeletal anomalies mainly an increased incidence . . . in deviations in the origin of small arteries from the aorta . . ." Stenosis of the aortic arch and interventricular septal defects were seen in pups of treated rats, in addition to increases in stillborn offspring. None of the control animals that did not get sibutramine had any of these cardiovascular birth defects. In another rat study, pups from untreated females nursed by treated mothers tended to have lower body weights indicating a potential for transfer of drug to the breast milk and adverse effects as a result.[7]

ADVERSE EFFECTS SEEN IN POST-MARKETING REPORTS

Our analysis of the FDA Adverse Event Reports (AERS) database, from launch through March 2003, yielded 54 reports with the terms of "Complications of maternal exposure" or "Maternal drugs affecting fetus" where sibutramine was listed as the primary suspect drug. Since fetal harm is not mentioned in the label or in the medical literature, it was quite surprising to find so many reports, including four babies with cardiovascular birth defects including:

> 1) Bicuspid aortic valve with cardiac murmur; 2) cardiomegaly [large heart], congenital anomaly; 3) congenital heart disease; 4) ventricular hypoplasia (underdeveloped heart chamber) (Appendix Table 3).

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[6] David Hertig, FDA Pharmacology Review, October 3, 1996; p.65.
[7] Ibid; p.36.

These clinical findings are of great concern because of the cardiovascular birth defects in two different animal species tested with the drug (see above section on toxicology studies).

In addition to the cardiovascular defects in infants, there are reports of spontaneous abortions, stillbirths, and congenital malformations including those of the central nervous system (hydrocephalus, Chiari malformation, brain neoplasm, spina bifida).

The label provides little indication of any specific potential harm to patients from taking sibutramine during pregnancy, simply stating: "The use of Meridia during pregnancy is not recommended" and adds that, "Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy." This wording could indicate to physicians and patients that sibutramine use during pregnancy was not a high concern since it is unaccompanied by any specific data. Nowhere in the list of post-marketing reports of adverse events in the label is there any mention of such harm nor could we find any reports in the medical literature.

Conclusions:

Prior to its approval, the FDA Medical Officer wisely warned of the dangers of sibutramine: "The extended use of Sibutramine as currently proposed by the Sponsor, I feel, may likely subject a significant portion of relatively healthy, overweight individuals to substantial risk for cardiovascular events."[8] The Team Leader was also concerned about the increase in blood pressure, warning that, "Without some information allowing reasonably accurate identification of patients likely to develop substantial blood pressure elevations on this drug, it should be regarded as not approvable.... Benefits have not been shown to outweigh risks."[9] Now, with at least 49 cardiovascular deaths reported, most among relatively young women and men, plus 124 people with cardiovascular adverse reactions serious enough to require hospitalization, it is even clearer that sibutramine should not continue to be marketed.

An additional reason to ban sibutramine is its effect on the developing fetus. The FDA pharmacology reviewer provided an early warning by citing cardiac malformations in the offspring of rats and rabbits treated with the drug during pregnancy (see above). Since sibutramine was marketed, there has been a continuing series of reports of fetal harm including reports of four babies born with cardiovascular abnormalities.

It was the hope of FDA management that blood pressure screening before drug treatment followed by monitoring for the first weeks of use could ensure the safe

[8] Eric Colman, M.D., Medical Officer, Memo, October 11, 1996.
[9] Gloria Troendle, M.D., Team Leader Review, October 11, 1996.

use of sibutramine; this provided the rationale that led to its approval.[10] However, the steadily increasing numbers of cardiovascular deaths and serious cardiovascular adverse events being reported to the FDA clearly do not support that supposition. The additional harm being done to pregnant women and their offspring is an additional significant source of concern.

We again strongly urge that sibutramine should be banned: the adverse events are serious, the number of victims is rising rapidly, and the efficacy is minimal. At the time of the drug's approval, it was announced that the average weight loss in obese people taking the drug for one year--beyond the weight loss in those getting a placebo--was only 6 1/2 pounds in the group taking 10 mg of the drug.[11]

We do not advocate labeling changes for minimizing this drug's risk since such changes have not been shown to be helpful in reducing drug risk with other drugs. The FDA's Drug Risk Assessment Group, along with individuals from medical schools and health care organizations, have analyzed the consequences of post-marketing label changes and have clearly shown that black-box warnings and "Dear Health Care Professional" letters had little or no beneficial effect in reducing the risk of two drugs studied: troglitazone and cisapride.[12,13] Both later had to be removed from the market. As a result, it seems extremely unlikely that "Dear Doctor" letters or label changes would stem the number and severity of the adverse events occurring with sibutramine, especially when they are in conflict with aggressive marketing practices, including direct to consumer advertising. There is no justification in continuing to market a drug that provides minimal weight reduction while increasing the likelihood of injury and death.

Sincerely,

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Elizabeth Barbehenn, Ph.D.
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Peter Lurie, M.D., MPH
Deputy Director

Sidney Wolfe, M.D.
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[10] Solomon Sobel, M.D., Division Director, Memo, November 18, 1997.
[11] FDA Approves Sibutramine to Treat Obesity. FDA Talk Paper. November 24, 1997. At a dose of 15 mg, the average weight loss, beyond placebo, was only 10 1/2 pounds.
[12] Graham DJ, Drinkard CR, Shatin D, et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001;286:831-833.
[13] Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride. JAMA 2000;284:3036-3039.

APPENDIX

Table 1. Sibutramine-Associated Cardiac Deaths (10/01 through 3/03)

Age/sex	Adverse Event
28/F	Cardiac arrest
30/F	Myocardial Infarction
37/F	Cardio-respiratory arrest
37/F	Cardio-respiratory arrest
37/F	Cardiac arrest
39/F	Cardiac arrest; tachycardia
39/F	Cardiac arrest
40/F	Myocardial Infarction
40/M	Myocardial Infarction
42/F	Myocardial Infarction
43/M	Myocardial Infarction
43/M	Sudden death unexplained
45/M	Myocardial Infarction
47/M	Chest pain
48/M	Cardiomyopathy
48/M	Myocardial Infarction; palpitations
50/M	Myocardial Infarction
50/F	Cardiomegaly
50/M	Myocardial Infarction
51/M	Myocardial Infarction
61/F	Cardio-respiratory arrest
65/M	Myocardial Infarction
65/F	Ruptured cerebral aneurysm
66/F	Arrhythmia
67/F	Myocardial Infarction
67/M	Myocardial Infarction
U/F	Arrhythmia
U/F	Hypertension
U/M	Myocardial Infarction
U/F	Cardio-respiratory arrest

Table 2. Sibutramine-associated Cardiac Adverse Events (all outcomes excluding death) (10/01 through 3/03: chronological order)

Age/sex	Adverse Event	Outcome
31/M	Chest pain	Hospitalization
64/F	Myocarditis	Required intervention
42/M	Myocardial infarction	Required intervention
61/F	Arterial aneurysm	Hospitalization
54/F	Cerebral infarction	Hospitalization
U/F	Tachycardia; cardiac failure	Required intervention
55/M	Tachycardia; atrial fibrillation; cardiomyopathy	Life threatening
17/F	Intracranial pressure increased	Hospitalization
29/F	Hypertension	Hospitalization
69/F	Tachycardia;hypertension	Required intervention
48/F	Hypertension; tachycardia	Required intervention
40/F	Sinus tachycardia; pulmonary hypertension	Required intervention
62/F	Cardiac failure; pulmonary hypertension	Hospitalization
62/F	Cardiac disorder; chest pain	Hospitalization
31/F	Blood pressure increased; chest pain; pulmonary hypertension	Hospitalization
41/F	Heart rate increased; blood pressure increased	Required intervention
U/F	Arrhythmia; syncope	Required intervention
62/M	Hypertension aggravated	Hospitalization
U/F	Cardiac disorder	Hospitalization
68/M	Transient ischemic attack	Required intervention
57/F	Cardiomegaly; chest pain; arrhythmia	Hospitalization
47/M	Hypertension	Disability
U/F	Pulmonary hypertension	Hospitalization
50/F	Cardiac failure congestive	Required intervention
42/M	Chest pain	Required intervention
70/F	Cerebrovascular accident	Hospitalization
44/F	Arrhythmia; tachycardia; atrial flutter	Required intervention
39/M	Atrioventricular block; atrial flutter; atrial fibrillation	Hospitalization
34/F	Cerebrovascular accident	Hospitalization
35M	Hypertension	Hospitalization
27/F	Chest pain	Unknown
U/F	Cerebrovascular acident	Other
31/F	Blood pressure increased	Hospitalization
56/F	Blood pressure increased; chest pain	Required intervention
31/F	Myocardial infarctionl	Hospitalization
47/F	Cardiac disorder; arrhythmia; blood pressure increased	Hospitalization

49/F	Sinus arrhythmia; cardiomyopathy; ventricular tachycardia	Hospitalization
U/F	Arrhythmia; heart rate increased	Hospitalization
U/F	heart rate increased; blood pressure fluctuation	Required intervention
68/M	Cerebrovascular accident	Life-Threatening
29/F	Chest tightness	Required intervention
50/F	Heart rate increased; Blood pressure increased	Hospitalization
U/F	Cerebrovascular accident	Other
42/M	Blood pressure increased	Other
50/F	Chest pain; blood pressure increased; palpitations	Hospitalization
52/F	Transient ischemic attack	Other
51/F	Tachycardia	Life-Threatening
13/M	QT prolonged	Other
32/F	Hypertension	Hospitalization
35/F	Pulmonary hypertension primary	Hospitalization
46/M	Blood pressure increased	Hospitalization
53/M	Ventricular extrasystoles	Other
U/F	Cardiac arrest	Required intervention
32/F	Cardiac murmur; palpitations	Other
U/U	Cardiac failure	Hospitalization
48/F	BP increased; tachycardia	
44/M	Chest pain; heart rate irregular	Required Intervention
60/M	Cardiac arrest; acute myocardial infarction	Hospitalization
42/F	Chest discomfort; ECG PR shortened	Life threatening
38/F	Cardiac failure; ventricular fibrillation	Hospitalization
47/M	Chest pain; vasovagal attack	Hospitalization
47/F	Hypertension; hemorrhagic stroke	Hospitalization
59/F	Cardiac failure	Required Intervention
47/F	Palpitations; collapse	Hospitalization
U/F	Diastolic dysfunction; hypertension; tachycardia	Required Intervention
44/F	Cerebrovascular accident hypertension	Hospitalization
73/F	Vasovagal attack	Required Intervention
48/F	Cerebral infarction	Hospitalization
63/F	Pulmonary hypertension; aortic valve stenosis; cardiomegaly	Hospitalization
48/M	Chest pressure sensation; ventricular extrasystoles	Hospitalization
38/F	Cardiac arrest	Hospitalization
53/F	Acute myocardial infarction; cerebral infarction	Hospitalization
U/M	Cardiac failure congestive	Hospitalization

39/F	Accelerated idioventricular rhythm	Hospitalization
41/M	Chest pain; ST-T ECG change	Hospitalization
63/F	Left ventricular hypertrophy	Required Intervention
42/M	Hypertension	Life threatening
38/F	Cardiac failure	Hospitalization
U/M	Arrhythmia; ejection fraction decreased	Required Intervention
63/F	Pulmonary hypertension; cardiac disorder	Hospitalization
29/U	Hypertension	Required Intervention
37/F	Blood pressure increased	Required Intervention
47/F	Blood pressure increased; Cerebral hemorrhage	Hospitalization
62/F	Cardiac failure; cardiomyopathy; tachycardia	Required Intervention
54/M	Syncope	Required Intervention
35/F	ECG: P wave abnormal; Palpitations	Required Intervention
51/F	Cardiac murmur; cardiomyopathy	Required Intervention
48/F	ECG abnormal; tachycardia	Required Intervention
U/M	Atrial tachycardia	Required Intervention
U/F	Atrial tachycardia	Required Intervention
41/F	Blood pressure fluctuation	Hospitalization
U/F	Arrhythmia	Life threatening
U/F	Cerebrovascular accident; stroke	Hospitalization
34/F	Blood pressure increased; palpitations	Hospitalization
48/F	Hypertension; tachycardia	Required Intervention
37/F	Hypertension	Life threatening
42/F	Chest pain; dizziness	Hospitalization
42/M	Hypertensive crisis	Required Intervention
53/U	Atrial fibrillation; palpitations	Hospitalization
41/M	Myocardial Infarction	Hospitalization
49/M	Atrial fibrillation	Hospitalization
35/F	ECG: P wave abnormal; palpitations	Required Intervention
42/M	Hypertension	Required Intervention
22/F	Chest pain; dizziness	Hospitalization
42/M	Hypertension	Required Intervention
61/F	Arrhythmia; chest pain	Hospitalization
U/F	Chest pain; cerebrovascular accident; tachycardia	Hospitalization
54/F	Cerebral infarction; tachycardia	Hospitalization
U/F	Heart rate increased	Required Intervention
54/F	Cerebral infarction; tachycardia	Hospitalization
22/F	Chest pain; dizziness	Hospitalization
40/F	Heart rate increased	Required Intervention
U/M	Tachycardia	Required Intervention
34/F	Blood pressure increased; palpitations	Hospitalization
U/F	Chest tightness; clamminess	Required Intervention
34/F	Transient ischemic attack	Hospitalization

40/F	ECG abnormal; chest pain; heart rate increased	Hospitalization
30/F	Ischemia	Required Intervention
U/F	Supraventricular tachycardia	Hospitalization
45/F	Hypertension	Required Intervention
55/M	Cardiovascular disorder	Required Intervention
40/F	Chest tightness	Hospitalization
60/F	Myocardial ischemia	Life threatening
58/M	Chest pain	Hospitalization
38/F	Chest pain; dyspnea	Required Intervention
66/F	Atrial fibrillation; right ventricular failure	Hospitalization

Table 3. Effects on fetus in patients using sibutramine (Meridia) February 1998 through March 2003 (chronological order)

MaternalAge/ Fetal or Infant Sex	Adverse Event	Outcome
43/F	Premature baby	Hospitalization
U/F	Abortion missed	Other
U/M	Aortic valve stenosis; disorder neonatal	Congenital anomaly; Hospitalization
31/F	Abortion spontaneous	Other
21/F	Stillbirth; omphalitis	Other
33/F	Intra-uterine death; abortion spontaneous	Other
30/F	Musculoskelet-al disorder; abortion induced	Other
34/F	Abortion spontaneous	Other
U/M	Death neonatal; congenital heart disease	Death
U/M	Erb's palsy; shoulder dystocia; delayed delivery	Disability
U/M	Pre-auricular sinus congenital; C-section	Congenital anomaly
U/F	Ovarian disorder	Other
30/F	Abortion spontaneous	Other
32/F	Vaginal hemorrhage; abortion threatened	Other
30/F	Abortion spontaneous; cervical incompetence	Other
39/F	Abortion induced	Required Intervention
32/F	Ultrasound antenatal screen abnormal; aborted pregnancy	Required Intervention
30/F	Unwanted pregnancy; abortion induced	Required Intervention
U/M	Congenital foot malformation; eye deformity; intrauterine death; hydrocephalus	Death; congenital anomaly
29/F	Congenital hydroce-phalus; abortion induced	Unknown
U/U	Down's syndrome; abortion induced	Death congenital anomaly
37/F	Neonatal disorder; premature baby	Hospitalization
U/F	Pulmonary edema neonatal; sleep apnea syndrome	Hospitalization
U/F	Ventricular hypoplasia	Death; congenital anomaly

12/U	Fetal growth retardation; premature baby	Death
32/F	Premature baby; pre-eclampsia	Hospitalization
U/U	Premature baby; death	Death
38/F	Spontaneous abortion	Required Intervention
39/F	Spontaneous abortion	Other
29/F	Congenital hydro-cephalus; chromosome abnormality	Required Intervention
U/M	Congenital foot malformation; hydroce-phalus; syndactyly	Death
37/F	Fetal disorder; abortion induced	Required Intervention
37/F	Down's syndrome; abortion induced	Required Intervention
U/F	Chiari malformation; nervous system anomaly; spina bifada; Abortion induced	Death
38/F	Abortion spontaneous	Required Intervention
U/U	Fetal growth retardation; hypertension	Death
39/F	Abortion spontaneous	Required Intervention
28/F	Abortion induced; congenital heart disease	Required Intervention
U/U	Cardiomegaly; congenital abnormality	Death
40/F	Abortion spontaneous	Required Intervention
38/F	Neonatal apneic attack; testicular disorder; premature baby	Hospitalization
39/F	Abortion induced	Required Intervention
25/F	Unknown	Required Intervention
31/F	Unintended pregnancy	Required Intervention
U/M	Cardiac murmur; hemoglobin decreased; premature baby	Hospitalization
U/M	Bicuspid aortic valve; cardiac murmur; premature baby	Hospitalization
21/F	Unintended pregnancy	Required Intervention
U/U	Cerebellar tumor	Congenital abnormality
U/F	Congenital abnormality; brain neoplasm; abortion induced	Required Intervention
U/F	Pyelocal-iectasis; C-section	Congenital anomaly
U/M	Renal agenesis	Required Intervention
21/F	Chiari malformation; abortion induced	Unknown
U/U	Chiari malformation; abortion induced	Congenital anomaly