Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

March 19, 2002

Tommy Thompson, Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Thompson,

Public Citizen, a nationwide consumer organization, with a membership of more than 130,000, petitions the 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 ban the unacceptably dangerous prescription diet drug Meridia (sibutramine, Knoll Pharmaceuticals/Abbott). According to the FDA data base, since its launch in early 1998 sibutramine has now been associated with 29 deaths including 19 from cardiovascular adverse effects in people using this minimally effective drug.[1] Two weeks ago, its use was suspended in Italy because of two cardiovascular deaths and its safety is currently under review in other European countries where, in the UK and France alone, there have been a total of 103 serious adverse reaction reports in people using the drug including two deaths in Britain.[2]

Prior to its approval in 1997, a FDA advisory committee voted five to four that the benefits of sibutramine did not outweigh the risks. The FDA medical officer who reviewed the drug wrote that "sibutramine has an unsatisfactory risk-benefit ratio and therefore this Reviewer recommends non-approval of the original submission." The concern of both the advisory committee and the FDA medical officer was based on the fact that sibutramine significantly increases blood pressure and heart rate in many people. When announcing its seriously mistaken approval of sibutramine in November 1997, the FDA stated 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.[3]

This is the fifth petition we have filed with the FDA to ban a drug since 1996. The last four were for the diet drug Redux (banned September 1997 after our April 1996 petition), the diabetes drug Rezulin (banned in March 2000, one year and eight months after our July 1998 petition), the antibiotic Trovan (severely restricted in the U.S. and banned in Europe in June 1999 after our earlier June petition), and Lotronex, a drug for irritable bowel syndrome (banned in November 2000, three months after our August 2000 petition). For all of these other four drugs, as with sibutramine, there was also clear evidence of danger before FDA approval.

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[1] FDA adverse reaction reports (AERS) through September 2001.

[2] Abbott's Reductil [UK name for sibutramine] linked to two deaths in Britain. Reuters Health March 15, 2002.

[3] 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.

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As mentioned above, the effect of sibutramine in promoting weight loss is meager and it is not known if this drug, or any diet drug for that matter, can be taken safely for a long enough period of time to reduce the morbidity and mortality associated with obesity. The editors of the highly respected independent American source of drug information, *The Medical Letter on Drugs and Therapeutics*, written for physicians and pharmacists, concluded in their review of sibutramine: "Medical Letter consultants advise against using the drug."[4] More recently, the French medical journal, *Prescrire International*, concluded that "Sibutramine...has amphetamine-like side effects" and "In practice sibutramine currently has no place in the management of obesity."[5]

ACTION REQUESTED

The removal of sibutramine from the market.

STATEMENT OF GROUNDS

Our petition is based on the following information:

Placebo-controlled clinical trials prior to approval showed a significant increase in blood pressure, heart rate and abnormal electrocardiograms.

There have been 397 serious adverse reactions reported to the FDA since sibutramine was first marketed in February 1998 up through the end of September 2001. Of these 397 serious adverse reactions, 152 patients were hospitalized and 29 patients died, including 19 with cardiovascular causes of death such as heart attacks. There were also 143 patients in whom an arrhythmia was reported.

The FDA medical officer coordinating the review of the New Drug Application for sibutramine concluded on May 10, 1996 ". . . sibutramine has an unsatisfactory risk-benefit ratio, and therefore this Reviewer recommends non-approval of the original submission of NDA 20-632."[6]

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted on September 26, 1996 5 to 4 against sibutramine's approval when asked "Do the benefits of sibutramine outweigh the risks?" The advisory committee also voted 8 to 0 that the pressor (high blood pressure-raising) effect of subutramine was "clinically important."[7]

Blood pressure screening may therefore not prevent those at risk of sibutramine's dangerous increases in blood pressure from receiving the drug.

In one study submitted by Knoll to the FDA, patients taking sibutramine were three times more likely to experience clinically significant ECG (electrocardiogram) changes than patients taking placebo.

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[4] Sibutramine for obesity. *The Medical Letter on Drugs and Therapeutics* 1998;40:32.
[5] Prescrire International. 2001. October;10:140-145.
[6] Sibutramine (Meridia) Medical Officer Review, Eric Coleman, M.D., May 10, 1996, page 162.
[7] Transcript of the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee, September 26, 1996, page 281.

THE FDA MEDICAL OFFICER'S REVIEW OF SIBUTRAMINE

The FDA Medical Officer responsible for coordinating the review of sibutramine was unequivocal in his concern about this drug's safety that the risks of sibutramine outweigh its benefits and that it should not be approved. In particular, his safety concerns centered on sibutramine's paradoxical effect in significantly raising blood pressure even though patients taking the drug were losing weight.

The following are pertinent comments taken from the FDA's review of clinical trials on sibutramine:

> To date, there have been eight reported cerebrovascular accidents [strokes]: Seven of these subjects were taking sibutramine and one was receiving placebo.
>
> . . the safety data indicate a possible to probable drug-related risk for several serious adverse events cardiac arrhythmia, cerebrovascular accident, acute interstitial nephritis, thrombocytopenia, and bleeding disorders. Furthermore, the safety data highlight the paradoxical increase in blood pressure despite weight loss in sibutramine-treated patients.
>
> Sibutramine's most worrisome safety issue centers on its effects on the major obesity-related co-morbidities, particularly blood pressure. A disturbing result of the dose ranging study BPI 852, and its open-label extension 852X, was the paradoxical increase in blood pressure despite weight loss. Although the subjects in BPI 852 and 852X were normotensive at baseline, one would expect a reduction in blood pressure following weight loss in obese individuals.[8]

In his summary, before recommending that the drug not be approved the Medical Officer said:

> ". . . the 10 and 15 mg doses of sibutramine satisfy the minimum weight-loss criteria and duration of study as defined in the Guidance, however, sibutramine does not improve, and in some cases it aggravates major obesity-related co-morbidities."[9]

The results of a study submitted to the FDA by Knoll illustrate the safety problems of sibutramine in regard to increases in both heart rate and blood pressure. This study is known as BPI 852 and was a 24-week, double blind, placebo controlled, dose ranging study in 1,047 obese patients.

Table 1 summarizes the cardiovascular events that occurred more frequently in the sibutramine treated patients compared to the placebo subjects in study BPI 852. These adverse reactions were also among those that most frequently led to premature termination of treatment with sibutramine.

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[8] Sibutramine (Meridia) Medical Officer Review, Eric Coleman, M.D., May 10, 1996, pages 159-160.
[9] Sibutramine (Meridia) Medical Officer Review, Eric Coleman, M.D., May 10, 1996, page 161.

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Table 1- The Percentage of Subjects Experiencing Adverse Cardiovascular Reactions in Study BPI 852

Adverse Event	Sibutramine	Placebo
Rapid Heart Rate	2.8%	0.5%
Palpitations	3.1%	1.2%
High Blood Pressure	2.1%	0.8%
Vasodilatation	2.6%	0.8%

The Medical Officer also wrote:

> Of concern are the potential effects of sibutramine on cardiac conduction (i.e., arrhythmias). Sibutramine's inhibition of the reuptake of norepinephrine and resultant increase in sympathetic tone provide the pharmacological basis for this concern. The Knoll medical monitor determined that 31 last on-treatment ECGs from 2473 patients had clinically significant changes from their respective baseline ECGs. Twenty-eight of the 31 abnormalities were from subjects taking sibutramine and 3 were from placebo patients. The ratio of subjects taking sibutramine to those on placebo was 3.0...The majority of these abnormalities were arrhythmias. A consultant cardiologist felt that 5 of the 28 ECGs represented clinically significant changes. These changes included frequent ventricular ectopic beats, atrial fibrillation, left bundle branch block, and T wave changes. Although the precise number of subjects who had sibutramine-induced ECG abnormalities is difficult to determine with great precision, the drug's effect on pulse and blood pressure raise concern if the drug is taken by a large number of obese subjects, many of whom have occult coronary artery disease.[10]

THE ADVISORY COMMITTEE DELIBERATIONS

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee met on September 26, 1996 to discuss sibutramine.

During the discussion, the following comments were made by advisory committee members or FDA staff:

". . . data from 239 additional hypertensive patients treated in other placebo controlled obesity studies. . . . The systolic blood pressure in the placebo group decreased 7.6 mm of Hg compared to a decrease of 4.5 mm for the 10 mg group."[11]

Referring to SB 1047, a one-year study of sibutramine in which those who lost more than 5 kg of body weight had an increase in systolic blood pressure of more than 10 mm (1.4% of placebo pts and 12% of all sibutramine subjects) p=0.0006, FDA asked ". . . can you effectively and

[10] Sibutramine (Meridia) Medical Officer Review, Eric Coleman, M.D., May 10, 1996, page 130.

[11] Transcript of the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee, September 26, 1996, page 105.

easily and early-on in treatment screen these individuals out so that you don't expose someone to potentially a year of blood pressures in this range? ....I think these data...suggest that there is a subgroup of patients who have a substantial increase in bp [blood pressure] and that is of concern, [12]

When asked the question "Do the benefits of sibutramine outweigh the risks?" the committee voted 5 to 4 that they did not.[13] Of the nine committee members, there were only two wholly unqualified votes that the benefits of sibutramine outweigh the risks. In response to the question "Is the pressor [high blood pressure-causing] effect of sibutramine clinically important?," the committee voted 8 to 0 that it was.

POSTMARKETING ADVERSE DRUG REACTIONS WITH SIBUTRAMINE

Sibutramine was approved on November 22, 1997 and was on pharmacy shelves in February 1998. Using the Freedom of Information Act (FOIA) Public Citizen obtained a computerized version of all reports of serious adverse drug reactions associated with the use of the drug through September 30, 2001.

In this period there were 397 reports of people with serious adverse reactions, of whom 152 were hospitalized and an additional 29 patients died, 19 of cardiovascular causes such as heart attacks. Included in the 19 cardiac deaths were 10 people who were 50 or younger, including three women under the age of 30. There were also 143 patients in whom an arrhythmia was reported.

A DANGEROUSLY LOW APPROVAL STANDARD HAS LED TO NEEDLESS DEATHS AND INJURIES FROM DIET DRUGS

Over 30 years ago, in June 1968, FDA Medical Officer Dr. Robert O. Knox refused to approve the New Drug Application (NDA) for a diet drug. This disapproval touched off a dispute between the FDA and the drug's manufacturer, A.H. Robbins, that eventually led to the drug's approval and Dr. Knox's transfer to another area within the Agency. His reason: obesity is a chronic disease and there is no evidence that these drugs affect the course of the disease over the long term.[14]

The drug Dr. Knox refused to approve was fenfluramine (Pondimin), a drug that ultimately became the "fen" portion of the notorious "fen/phen" combination, that was removed from the market on September 15, 1997 because it caused heart valve damage and a potentially fatal adverse reaction of the lungs known as primary pulmonary hypertension.[15]

Thirty years of experience with diet drugs has clearly vindicated Dr. Knox's views. If his

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[12] Transcript of the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee, September 26, 1996, page 178.

[13] Transcript of the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee, September 26, 1996, page 281.

[14] Department of Health, Education, and Welfare. Investigation of Allegations Relating to the Bureau of Drugs, Food and Drug Administration, Review Panel on New Drug Regulation. April 1977. This investigation has come to be known as the Dorsen Report after Norman Dorsen, Professor of Law, School of Law New York University who chaired the Review Panel. The account of the controversy involving Dr. Knox is excerpted from this report.

[15] Department of Health and Human Services. Food and Drug Administration. FDA announces withdrawal of fenfluramine and dexfenfluramine. September 15, 1997.

recommendation had been heeded in 1968, and the FDA adopted a standard that required the demonstration of a health benefit from these drugs, hundreds of millions of dollars would have been saved and an immeasurable number of patients would have been spared serious harm and death.

CONCLUSION

The known serious risks of sibutramine might be acceptable if there were evidence that it prevented one stroke or heart attack or prolonged the life of a single patient. Such evidence is lacking for sibutramine as well as for other diet drugs, leaving patients with only the risk of injury from their use and expensive drug bills. This disproportionate risk compared to any known therapeutic benefit of sibutramine was seen by the FDA medical officer and the members of the Endocrinologic and Metabolic Drugs Advisory Committee who recommended against its approval.

Sibutramine is a drug that should never have been approved, and in the interest of the safety of the American public it must come off the market now. The FDA must reexamine the episode of Dr. Knox and fenfluramine and reject an approval standard for diet drugs that only requires short term studies which demonstrate the statistical superiority of a drug over a placebo.

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.

ENVIRONMENTAL IMPACT

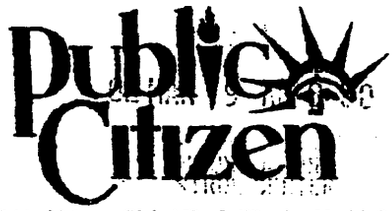
Nothing requested in this petition will have an impact on the environment.

Sincerely,

Sidney M. Wolfe, M.D.
Director

Larry D. Sasich, Pharm.D., M.P.H., FASHP
Staff Researcher

Elizabeth Barbehenn, Ph.D.,
Staff Researcher
Public Citizen Health Research Group



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Joan Claybrook, President

FAX Transmittal Form

To: Tommy Thompson **Number of pages:** 7
(including this one)

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From: Sidney Wolfe

Date: 3/19/02 **Fax Number:**
690-7203

Message:

ROUTING SLIP
GENERATED BY: HF-40
DATE: MAR 22, 2002

FDA CONTROL NUMBER: 02 1509 **TRACER #:** **OS #:** 0319020041

DATE OF CORRESPONDENCE: 03/19/02 **DATE INTO FDA:** 03/20/02

TO: TOMMY G THOMPSON, SECRETARY, HEALTH AND HUMAN SERVICES

FROM: SIDNEY M WOLFE, HRG, PUBLIC CITIZEN HEALTH RESEARCH GROUP
LARRY D SASICH, PUBLIC CITIZEN
ELIZABETH BARBEHENN, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

SYNOPSIS: REQUESTING THAT FDA IMMEDIATELY BAN THE UNACCEPTABLY DANGEROUS PRESCRIPTION DIET DRUG MERIDIA (SIBUTRAMINE, KNOLL PHARMACEUTICALS/ABBOTT)

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REFERRALS FROM HF-40

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HFA-305	BUTLERJ	NECESSARY ACTION	04/02/02

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

From:	**Sidney M. Wolfe**	*OS#:*	**031920020041**
Organization:	**Public Citizen**	*Date on Letter:*	**3/19/02**
City/State:	**Washington DC**	*Date Received:*	**3/19/02**
On Behalf Of:		*Type:*	**Major Organization**

Subject: **(Faxed copy) -- Co-signed by Larry D. Sasich and Elizabeth Barbehenn. Petitions the 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 ban the unacceptably dangerous prescription die drug Meridia (sibutramine, Knoll Pharmaceuticals/Abbott).**

Assigned to:	**FDA**	*Dep.ES:*	**Dick Eisinger**
PC:	**Tom Kuchenberg**	*Date Assigned:*	**3/19/02**
Action Required:	**Direct Reply**	*Date Reassigned:*	
		Reply Due Date:	**4/2/02**

Info Copies To: **Kuchenberg, Thomas (HHS/OS); SWIFT, ASBTF; SWIFT, ASL; SWIFT, ASPA; SWIFT, ASPE; SWIFT, DEP; SWIFT, DXS; SWIFT, ESS; SWIFT, IGA; SWIFT, NIH; SWIFT, OGC; SWIFT, OPHS; SWIFT, SAMHSA**

Interim (Y/N):	**No**	*Date Interim Sent:*	

Comments: **Downgraded to Direct Reply per Tom Kuchenberg 3/19/02-gpe.**

File Index:	**PO-4-5**	*CCC:*	**Gloria Ellis**

02-1509