DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 9 2005

Sidney M. Wolfe, M.D.
Elizabeth Barbehenn, Ph.D.
Larry D. Sasich, Pharm.D., M.P.H., FASHP
Public Citizen Health Research Group
1600 20th Street, N.W.
Washington, D.C. 20009-1001

Re: Docket No. 2002P-0120/CP1 and SUP1

Dear Drs. Wolfe, Barbehenn, and Sasich:

This responds to your citizen petition, dated March 19, 2002 (Petition), requesting that the Food and Drug Administration (FDA) remove Meridia (sibutramine) from the market because of adverse events associated with the drug. It also responds to the supplement you submitted on September 3, 2003 (Supplement), updating the adverse event data for sibutramine covering the 18-month period subsequent to your petition (October 1, 2001, through March 31, 2003). The supplement also includes new information on fetal adverse events. For the reasons discussed below, your petition is denied. However, we continue to monitor the safety profile of sibutramine and have updated the risk management program for this drug product.

I. BACKGROUND

The Agency approved Knoll Pharmaceuticals' (Knoll) new drug application (NDA) for sibutramine (5 milligrams (mg), 10 mg, and 15 mg) for the management of obesity, including weight loss and the maintenance of weight loss, in November 1997 (NDA 20-632).[1] Sibutramine is approved in 72 countries and marketed in 65 countries worldwide.[2]

In March 2002, the Italian Ministry of Health temporarily suspended the marketing license for sibutramine in response to reports of serious adverse reactions, including two fatalities. Based on this experience, the Italian health authorities requested that the European Agency for the Evaluation of Medicinal Products' Committee for Proprietary Medicinal Products (CPMP) provide an opinion on whether sibutramine's marketing authorization should be maintained, changed, suspended, or withdrawn.[3]

---

[1] Abbott Laboratories (Abbott) acquired Knoll Pharmaceuticals on March 2, 2001, and currently holds the NDA for Meridia.

[2] Mexico was the first country to approve sibutramine, in November 1997. In January 1999, Germany became the first European country to approve sibutramine. The 10-mg and 15-mg once-daily doses are the most commonly marketed doses worldwide. With the exception of a few countries in Central America, the 20-mg dose of sibutramine has not been approved.

[3] Committee for Proprietary Medicinal Products, Opinion Following an Article 31 Referral. Sibutramine, December 2, 2002, available on the Internet at http://www.emea.eu.int/pdfs/human/referral/451402en.pdf.

After reviewing available efficacy and safety data, including the cases reported in Italy, the CPMP rendered a favorable opinion on June 27, 2002, and recommended that the marketing authorization for sibutramine be maintained. On August 28, 2002, the Italian Ministry of Health reinstated sibutramine's marketing license.

You submitted a petition requesting that FDA remove sibutramine from the U.S. market based on the events in Italy, other postmarketing adverse drug events, and the FDA approval history of sibutramine.

II. DRUG APPROVAL PROCESS

In the petition, you recount certain information about FDA's review process for sibutramine (Petition at 3). Specifically, you state that the FDA medical officer coordinating the review of the sibutramine NDA recommended non-approval based on an unsatisfactory risk-benefit ratio (Petition at 3). You also mention that FDA's Endocrinologic and Metabolic Drugs Advisory Committee (the advisory committee) did not support the approval of sibutramine (Petition at 5). You claim that a "dangerously low approval standard has led to needless deaths and injuries" (Petition at 5). As demonstrated below, we believe that FDA's review of the NDA for sibutramine followed standard procedures, and that the application met the statutory requirements for approval.

The NDA for sibutramine, a norepinephrine and serotonin reuptake inhibitor with sympathomimetic activity, was submitted to the Agency's Division of Metabolic and Endocrine Drug Products in August 1995. The sponsor was seeking approval of 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg once-daily doses of sibutramine for the treatment of obesity.

During the initial regulatory review cycle, the primary medical reviewer expressed concern about sibutramine's effect on blood pressure and eventually concluded that this single risk would likely outweigh the documented benefits of the drug, which in addition to weight loss itself, at that time, included secondary improvements in levels of HDL-cholesterol and triglycerides.

Given that the primary reviewing division's expertise did not include drugs that affect blood pressure, a consult on the sibutramine blood pressure data was obtained from the Agency's Division of Cardio-Renal Drug Products. In a response dated September 11, 1996, the consulting division acknowledged that sibutramine did cause a small pressor effect, but concluded that:

> Were sibutramine's effects on blood pressure the only basis for considering non-approval, such a decision would be a mistake, because potential long-term benefits of weight reduction could outweigh short-term risks of blood pressure elevation...

Dr. John Flack, a blood pressure expert then at the Bowman Gray School of Medicine, was retained by FDA as a consultant and asked to review the sibutramine blood pressure data. Dr. Flack agreed that the drug did increase blood pressure by an average of 1 to 3 mmHg, and while he did not comment on whether sibutramine should be approved, he stressed that the balance of sibutramine's risks vs. benefits would probably be unfavorable only in obese patients with uncontrolled hypertension, coronary artery disease, congestive heart failure, stroke, or cardiac arrhythmias, as these conditions would heighten the odds for adverse cardiovascular outcomes related to the drug's sympathomimetic activity.[4]

On September 26, 1996, the Endocrinologic and Metabolic Drug's Advisory Committee convened to publicly evaluate the data from the sibutramine NDA. Eight of the nine committee members agreed that the drug's effect on blood pressure was clinically important; however, all also believed that sibutramine was an effective weight loss drug, leading to a nearly evenly split vote on the question of whether the drug's benefits outweighed its risks.

Following the advisory committee meeting, FDA staff met internally and with Knoll on a number of occasions to discuss the pending sibutramine application. Although a wide range of opinions were expressed about the relative merits and shortcomings of the drug, all FDA staff concluded that sibutramine was an effective obesity agent, using the criteria in the Agency's draft *Guidance for the Clinical Evaluation of Weight-Control Drugs*.[5] Furthermore, FDA staff agreed that the drug's major risk was its effect on blood pressure. Discussion therefore focused on whether it was possible to identify practical ways to manage the blood pressure risk such that the drug's overall risk-benefit profile would prove favorable.

To this end, we requested that Knoll conduct additional, detailed analyses of the clinical trial blood pressure data, which would be considered during a second regulatory review cycle. These analyses confirmed two important findings that were crucial to rendering a final regulatory decision on the sibutramine NDA: (1) the risk for important elevations in blood pressure increased notably with the 20-mg and 30-mg doses of sibutramine, and (2) the risk for substantial increases in blood pressure was confined to a relatively small percentage of patients who could be identified through regular blood pressure monitoring.

---

[4] Food and Drug Administration, Endocrinologic and Metabolic Drugs Advisory Committee meeting transcript, September 1996, available on the Internet at http://www.fda.gov/ohrms/dockets/ac/meridia.htm.

[5] This FDA guidance states that an obesity drug will be considered effective if at least one of the following criteria is satisfied: (1) the mean weight loss between the drug- and placebo-treated patients after one year of treatment is at least 5 percent, or (2) the proportion of patients who lose at least 5 percent of their weight after one year of treatment is greater in the drug- and placebo-treated group. Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

In summary, the 26-month regulatory review of sibutramine was a deliberative, open, interactive, and admittedly complex process involving multiple FDA scientists from the Division of Metabolic and Endocrine Drug Products and the Division of Cardio-Renal Drug Products, a blood pressure expert from the Bowman Gray School of Medicine, and nine members of the advisory committee. There were certainly differences of opinion regarding sibutramine's overall risk–benefit profile, but all viewpoints and available data were taken into consideration before rendering a final regulatory decision on the NDA.

While sibutramine was not considered an appropriate drug for all obese patients, such as those with coronary artery disease, FDA ultimately concluded that when used in accordance with the approved labeling, the benefits of the lower doses of sibutramine would outweigh the potential increase of blood pressure, which can be monitored and, if necessary, treated, in appropriately selected obese patients.

The 5-mg, 10-mg, and 15-mg (but not the 20-mg and 30-mg) once-daily doses of sibutramine were approved on November 22, 1997, for the management of obesity, including weight loss and maintenance of weight loss, in obese patients with an initial body mass index ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

The approved professional and patient labeling includes prominent warnings that sibutramine substantially increases blood pressure in some patients and that regular monitoring of blood pressure is required when prescribing Meridia.[6] The labeling also clearly warns against the use of sibutramine in patients with uncontrolled hypertension or histories of coronary artery disease, stroke, heart failure, or cardiac arrhythmia.

III. PRE- AND POSTMARKETING ADVERSE EVENTS

You state that there was evidence of a safety risk before FDA approval of sibutramine (Petition at 3). You point out that in pre-approval clinical trials, subjects receiving sibutramine showed a significant increase in blood pressure, heart rate, and abnormal electrocardiograms. You express concern that blood pressure screening may not prevent those at risk for dangerous increases in blood pressure from being prescribed sibutramine.

You correctly state that data from the pre-approval trials indicated that sibutramine, relative to placebo, caused a 1- to 3-mmHg mean increase in blood pressure and a 4- to 5-beat-per-minute average increase in pulse rate, with a small percentage of patients taking sibutramine experiencing larger increases in blood pressure or pulse rate or both. These changes result from sibutramine's pharmacodynamic action inhibiting the neuronal reuptake of norepinephrine, leading to stimulation of the sympathetic nervous system.

---

[6] The approved labeling includes a table of the proportion of patients treated with sibutramine vs. placebo who developed substantial increases in blood pressure during the pre-approval clinical trials.

Predictably, sibutramine's stimulation of the autonomic nervous system also led more sibutramine- than placebo-treated subjects to develop tachycardia, premature atrial contractions, premature ventricular contractions (detected by electrocardiograms), and palpitations during the pre-approval trials. Importantly, however, there was no evidence that these events, or any other electrocardiographic findings, were associated with clinically significant outcomes or had any clinical relevance, as noted by the primary medical reviewer of the sibutramine NDA.[7]

A. Adverse Event Reporting System (AERS) Reports of Death and Other Serious Cardiovascular and Stroke Events

With respect to postmarketing adverse events associated with sibutramine, you state that there have been 397 serious "adverse reactions" reported to the FDA through the end of September 2001 (Petition at 2). Of these 397 serious adverse events, you state that 152 patients were hospitalized and 29 patients died, including 19 with cardiovascular causes of death (Petition at 2). In addition, you claim that the reports indicated arrhythmia in 143 patients (Petition at 2). In the supplement, you update your analysis of cardiovascular adverse events (Supplement at 1 to 2). Your updated analysis includes an additional 30 cardiovascular deaths reported from October 1, 2001, through March 31, 2003 (Supplement at 2). You state that the addition of these 30 cardiovascular deaths in just 18 months compared to the number in the first 44 months represents a significant increase in the rate of reports to FDA (Supplement at 2).

In response to the regulatory action taken by Italian officials and receipt of your petition and supplement, the Agency queried its AERS database[8] for (1) domestic reports of all-cause fatalities in patients exposed to sibutramine received during the time period November 22, 1997, through August 14, 2003 (Petition and Supplement); (2) domestic fatalities associated with a cardiovascular event during the time period November 22, 1997, through August 14, 2003 (Petition and Supplement); (3) domestic nonfatal serious cardiovascular events in patients exposed to sibutramine received during the time period November 22, 1997, through August 14, 2003 (Petition); and (4) domestic fetal or pregnancy-related adverse events associated with the use of sibutramine received during the time period November 22, 1997, through October 27, 2003 (Supplement).[9]

---

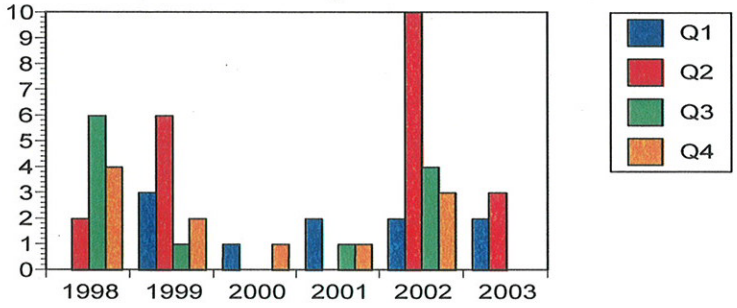
[7] Food and Drug Administration, Medical Officer's Review of the Original Submission of NDA 20-632 (sibutramine hydrochloride monohydrate), June 1996, available on the Internet at http://www.fda.gov/cder/foi/nda/97/20632_meridia.htm.

[8] The numbers we cite for all-cause deaths, deaths due to cardiovascular and stroke events, and nonfatal cardiovascular and stroke events, do not match the numbers you cite for several potential reasons: (1) the AERS search terms that we used may not be the same as the terms you used, (2) we limited our search to domestic cases, and (3) you did not state whether the number of cases in your petition are limited to unique patients or could include duplicates.

[9] The August 14 and October 27, 2003, dates reflect the cutoff dates of the Agency's AERS database queries.

During the reporting period from November 22, 1997, through August 14, 2003, a total of 54 domestic reports of death were submitted to AERS. As shown in the figure below,[10] the number of reports of death in patients exposed to sibutramine was highest during the first 2 years of marketing, declined thereafter, and transiently increased following the publicity over the Italian Ministry of Health's temporary suspension of sibutramine's marketing license and the submission of your citizen petition to FDA requesting that the drug be removed from the U.S. market. These are well-known patterns of post-approval adverse event reporting to passive drug safety surveillance systems such as AERS that reflect changes in the reporting environment (e.g., negative publicity) rather than true increases in the incidence of a specific drug-related adverse event.[11,12,13,14]

Figure - AERS Reports of Death in Patients Exposed to Sibutramine According to the Year and Quarter the Reports Were Received by FDA



Of the 54 reports of death, 30 were reportedly due to a cardiovascular cause including, but not limited to, myocardial infarction, congestive heart failure, viral cardiomyopathy, torsades de pointe, and sudden death. The remaining cases of death were secondary to a heterogeneous mix of conditions including, but not limited to, suicide, motor vehicle accident, respiratory failure, serotonin syndrome, pulmonary embolism, and "unknown cause."

During the reporting period from November 1997 through August 2003, there were a total of 224 domestic reports of serious nonfatal cardiovascular and stroke events

---

[10] The figure depicts the number of reports of death according to the date the report was received by FDA, not the date of the death.

[11] Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. In Rainsford KD, et al., eds., *Advances in Inflammation Research*, Vol. 6, New York: Raven Press, 1984, Pages 1-7.

[12] Hartnell NR, et al. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration, *Pharmacotherapy* 2004; 24:743-749.

[13] Collet JP, et al. Bias and confounding in pharmacoepidemiology. In Strom, BL, ed., *Pharmacoepidemiology*, 3rd edition, John Wiley and Sons Ltd, West Sussex PO19 1UD, England, 2000, Pages 765-769.

[14] Sachs RM, et al. An evaluation of spontaneous adverse drug reaction monitoring systems. *Am J Med* 1986; suppl 5B:49-55.

submitted to AERS in association with sibutramine use. Like the reports of death, the serious nonfatal cardiovascular and stroke reports included a broad mix of event terms, including viral cardiomyopathy, aphasia, cerebrovascular accident, ventricular tachycardia, chest pain, palpitations, anaphylactic shock, myocardial infarction, atrial fibrillation, hypotension, cardiac valve disease, and syncope. The pattern of, and explanation for, the reporting over time of the nonfatal cardiovascular and stroke events are similar to those for the fatal cases.

B. Interpretation of the AERS Reports of Death and Other Serious Cardiovascular and Stroke Events

Passive post-approval drug safety surveillance systems such as AERS are most reliable and useful for detecting signals of serious, previously unrecognized, rare adverse events.[15] For example, through passive surveillance, a signal for hemolytic anemia – a serious, rare, and unexpected disorder – was detected in young women taking the antibiotic temafloxacin for urinary tract infections.[16]

In contrast, passive drug safety reporting systems are not well-suited to assessing whether a drug increases the risk for commonly-occurring adverse events in the population for which the drug is approved. Myocardial infarction, stroke, heart failure, and arrhythmias are very common in patients with obesity.[17,18,19,20] And despite some biological/pharmacological plausibility of a relationship between a sympathomimetic drug like sibutramine and certain types of cardiac events, the high background risk for such events in the obese population render AERS reports of cardiovascular events in patients taking sibutramine of limited value in assessing whether the drug actually increases the risk for fatal or nonfatal cardiovascular adverse events.[21] In this setting (i.e., where the events of concern are associated with the underlying disease), epidemiological studies would also be limited in providing definitive results.

Moreover, the degree of documentation included in the reports of death and other serious cardiovascular and stroke events in subjects exposed to sibutramine varied greatly, from a single sentence submitted by non-healthcare professionals to pages of detailed medical histories, lists of concomitant medications, results of laboratory and

---

[15] Kennedy DL, et al. Spontaneous reporting in the United States. In Strom, BL, ed., *Pharmacoepidemiology*, 3rd edition, John Wiley and Sons Ltd, West Sussex PO19 1UD, England, 2000, Pages 151-174.

[16] Blum MD, et al. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis,* 1994; 18:946-950.

[17] Eckel RH, et al. Obesity and heart disease. *Circulation* 1997; 96:3248-3250.

[18] Must A, et al. The disease burden associated with overweight and obesity. *JAMA* 1999; 282:1523-1529.

[19] Manson JE, et al. Body weight and mortality among women. *N Engl J Med* 1999; 333:677-685.

[20] Huber HB, et al. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; 67:968-977.

[21] Rodriquez EM, et al. The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Safe* 2001; 10:407-410.

other specialized diagnostic tests, and autopsy findings, submitted by physicians. A sizable number of the AERS reports contained two sentences or less of descriptive information. This lack of detail compounded the difficult and highly subjective process of attempting to assign drug causality to commonly-occurring adverse clinical events.[22]

For these reasons, it is not possible, based on AERS data, to render a conclusion regarding whether sibutramine increases the rate of death or serious cardiovascular and stroke events.

IV. THE SIBUTRAMINE CARDIOVASCULAR OUTCOMES TRIAL

An unbiased, objective assessment of sibutramine's cardiovascular safety profile, particularly when used in obese patients with known or occult cardiovascular disease, can best be made through analyses of data from a large, randomized, controlled trial. The Sibutramine Cardiovascular Outcomes, or SCOUT study, is such a trial. SCOUT, underway in Europe, is a randomized, double-blind, placebo-controlled trial examining the incidence of fatal and nonfatal cardiovascular outcomes in approximately 9,000 obese patients at high risk for cardiovascular disease (e.g., a history of myocardial infarction) treated for up to 5 years with diet and exercise plus sibutramine or placebo. When completed, this study will provide precise estimates of the relative benefits and risks of sibutramine when added to lifestyle modification in a population of patients for whom sustained weight loss is highly desirable, but who, because of their underlying cardiovascular disease, are not at this time appropriate candidates for use of sibutramine outside of a controlled investigational setting.

As of April 22, 2005, approximately 8,000 patients had been enrolled into SCOUT. An independent data safety monitoring board is overseeing the conduct of the trial, and beginning in May 2005, they will be reviewing safety data on a monthly basis. FDA will be immediately notified and will take appropriate regulatory action if any serious safety concerns are identified during the study.

V. THE OVERALL BENEFITS VS. RISKS OF SIBUTRAMINE

While our response to your petition is focused on risk, it is important to recognize that the use of sibutramine in obese patients – who now represent nearly a third of all adults in this country[23] – is associated with a number of benefits in addition to weight loss itself, many of which have come to light following the drug's original approval in 1997.

In the Sibutramine Trial of Obesity Reduction and Maintenance (STORM), the longest study of sibutramine published to date, of 261 obese patients who completed the 2-year

[22] Koch-Weser J. The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 1977; 11:75-78.
[23] Flegal, KM, et al. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002; 288:1723-1727.

trial, 70 percent treated with sibutramine lost at least 5 percent of their baseline weight compared with approximately 48 percent of those treated with placebo; and 46 percent of the sibutramine-treated patients lost at least 10 percent of their baseline weight vs. approximately 20 percent of placebo-treated subjects.[24] Sibutramine-associated weight loss was accompanied by significant reductions in concentrations of serum triglycerides, VLDL cholesterol, insulin, C-peptide, and uric acid, as well as clinically meaningful increases in HDL cholesterol levels. The degree of improvement in these metabolic variables was proportional to the amount of weight lost.

Recent studies of obese patients with type 2 diabetes indicate that treatment with sibutramine for 12 to 52 weeks is associated with average weight loss ranging from 10 to 16 pounds, with significant lowering of $HbA1_c$ concentrations and, secondarily, with reduced requirements for diabetes medications in patients who received the drug for 52 weeks.[25,26]

A variety of studies published within the past few years reinforces the findings from the original NDA that sibutramine-related weight loss improves levels of HDL cholesterol, triglycerides, and in some cases the ratio of LDL-to-HDL cholesterol.[27]

Therefore, while sibutramine poses a risk of increased blood pressure in some patients, it also provides a number of secondary benefits in addition to weight loss. Moreover, just as the principal risk associated with sibutramine, increased blood pressure, is readily monitorable (and treatable), so too are the beneficial effects of the drug. This provides healthcare professionals with the ability to assess, on an ongoing and individual basis, the balance of benefits and risks of sibutramine use and to adjust dose, add adjunctive risk-modifying therapy, or to discontinue the drug as necessary.

VI. ADVERSE EVENTS INVOLVING FETAL TOXICITY

Your supplement includes a new category of adverse events affecting the fetus, including spontaneous abortions, stillbirths, and congenital malformations, such as heart and central nervous system malformations.

---

[24] James WP, et al. Effect of sibutramine on weight maintancence after weight loss: a randomized trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000; 356:2119-2125.

[25] Norris SL, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2004; 164:1395-1404.

[26] Redmon JB, et al. One-year outcome of a combination of weight loss therapies for subjects with type 2 diabetes: a randomized trial. *Diabetes Care* 2003; 9:2505-2511.

[27] Filippatos TD, et al. A review of the metabolic effects of sibutramine. *Cur Med Res Opin* 2005; 3:457-468.

Sibutramine is a Category C drug for which the Pregnancy section of the labeling reads:[28]

> **Pregnancy**
>
> *Teratogenic Effects-Pregnancy Category C*
>
> Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.
>
> No adequate and well controlled studies with MERIDIA have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

We have analyzed the data in your supplement and from our AERS database with respect to adverse drug experiences involving fetal toxicity associated with sibutramine. Between November 22, 1997, and October 27, 2003, AERS received a total of 34 domestic reports of pregnant women who had been exposed to sibutramine at some point during their pregnancies. The 34 reports were broadly categorized as spontaneous abortion, pregnancies with no outcome, therapeutic abortion, live births, and postnatal death. The following five birth defects were reported:

- Arthrogryposis x 1
- Aortic stenosis x 1
- Preauricular sinus of the right ear x 1
- Myoplastic left heart syndrome x 1
- Hypoplastic left ventricle x 1

According to the National Vital Statistics Reports, the most common defects in the United States in 1999 were musculoskeletal and connective tissue defects at 239.9 per 100,000 live births, followed by congenital heart defects at 119.8 per 100,000 live births,

[28] 21 CFR 201.57, available on the Internet at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57&SearchTerm=201%2E57 (May 20, 2005).

with other circulatory/respiratory anomalies at 140.6 per 100,000 live births.[29] Given that cardiac anomalies are among the most common birth defects in infants born in the United States, it is not surprising that three of the five birth defects reported to AERS involved the heart.

Because of the small number of AERS reports of birth defects in infants born to women exposed to sibutramine, the limited documentation included in the reports, and the lack of data regarding the number of pregnant women in the United States who have been exposed to sibutramine, it is not possible, based on this information, to render a conclusion regarding whether in utero sibutramine exposure increases the risk for birth defects or fetal toxicity. Nevertheless, based on preclinical data reviewed before the approval of the sibutramine NDA (these data form the basis of the language in the Pregnancy section of the current labeling) and information from two recently published case series of pregnant women exposed to sibutramine who delivered healthy infants, we believe that sibutramine is appropriately labeled as Category C and is not recommended for use during pregnancy.[30,31]

VII. RISK MANAGEMENT

During our review of the sibutramine AERS reports of deaths and serious cardiovascular and stroke events, we noted that some patients with a history of cardiovascular disease were prescribed sibutramine despite the labeled recommendation that such patients not receive the drug. While the prescribing of drugs at variance with the approved labeling is a practice that falls outside the Agency's regulatory purview, FDA has asked the sponsor to address the use of sibutramine in patients for whom there are limited efficacy and safety data in an updated risk management plan. This plan includes (1) a *Dear Healthcare Professional* letter stressing that patients with known cardiovascular disease should not be prescribed sibutramine and re-emphasizing the importance of monitoring blood pressure (and pulse) in all patients taking the drug; (2) revisions to the physician labeling and patient labeling to reinforce the proper use of the drug; and (3) an educational outreach program that is aimed at physicians to reinforce the message regarding which patients are not appropriate candidates for sibutramine.

---

[29] Ventura SJ, et al. Births: final data from 1999. National Vital Statistics Reports, 49:1, April 17, 2001, page 83; from the Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.

[30] Einarson A, et al. Exposure to sibutramine during pregnancy: a case series. *Eur J of Obstet Gynecol Reprod Biol* 2004; 116:112.

[31] Kadioglu M, et al. Sibutramine use in pregnancy: Report of two cases. *Birth Defects A Clin Mol Teratol* 2004; 70:545-546.

VIII. CONCLUSION

Following a 2-year regulatory review, FDA concluded that the benefits of sibutramine outweighed its risks for certain obese patients and approved the drug for the treatment of obesity on November 22, 1997, with labeling to warn physicians of the risks to certain patients and the need to monitor patients.

In our ongoing effort to maximize the safe and effective use of sibutramine, we have worked with the sponsor to update the physician and patient labeling to reinforce the appropriate population for and proper use of sibutramine (i.e., the need to regularly monitor blood pressure). An additional component of the risk management program includes an educational outreach program aimed at physicians who are likely to prescribe sibutramine.

Based on the previously described re-assessment of the original drug review process, an evaluation of data from AERS, and recently published studies, we continue to believe that sibutramine's overall risk-benefit profile supports it remaining available as a prescription drug for the treatment of appropriately selected obese patients. Your request that we remove sibutramine from the market is therefore denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research