Memorandum to the File
NDA 20-632
Meridia (sibutramine hydrochloride monohydrate)

DATE: October 4, 2010

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Director
Center for Drug Evaluation and Research (CDER)

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SUBJECT: Recommendation on a regulatory decision for Meridia

Executive Summary

Meridia (sibutramine) was approved for the treatment of obesity in 1997. In November 2009, preliminary results of a cardiovascular (CV) outcomes trial indicated that sibutramine increased the relative risk for major adverse cardiac events (MACE) by 16% in a population of older overweight and obese individuals, a population for whom treatment with sibutramine is warned against in the label. This increase in MACE was driven by non-fatal myocardial infarction and non-fatal stroke; there was no between-treatment difference in the risk of cardiovascular death or all-cause mortality.

While the sponsor has contended that patients at-risk for cardiovascular outcomes linked to sibutramine can be identified and CV risks mitigated, trial data did not support this finding. The trial showed evidence of harm without defining a population that may benefit. How the results of the trial would translate to the target (labeled) population is unknown. Clearly, if sibutramine is used in the target (labeled) population, the risk of non-fatal CV events may be exceedingly low; however, the sponsor did not show that there was a benefit to offset even a very low attributable risk for CV events and no other secondary manifestation of the illness of obesity seemed to be improved. Until the sponsor has identified a population in whom the benefit:risk profile for sibutramine is favorable, sibutramine should not remain on the market.

Therefore, both the Office of New Drugs and the Office of Surveillance and Epidemiology recommend that Meridia (sibutramine) should be removed from the U.S. market.

Regulatory History

Meridia was approved in the United States in November 1997 for weight loss and maintenance of weight loss in overweight or obese patients with an initial BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 in the presence of other cardiovascular risk factors. During the initial review of the application, it was determined that sibutramine satisfied one of the two efficacy criteria used by FDA to define benefit – approximately 60% of sibutramine-treated subjects versus approximately 30% of placebo-treated subjects lost greater than 5% of baseline body weight. Sibutramine's adverse effects on systolic and diastolic blood pressure (mean increases of 1-3 mm Hg) and pulse (mean increases of 4-5 bpm) were identified as the primary safety concerns; however, the benefit-risk profile of 3 (5, 10, 15 mg) of the 5 (5, 10, 15, 20, 30 mg) proposed doses was deemed favorable and the adverse effects monitorable.

The initial European Union approval of sibutramine was in January 1999, but due to concerns about the potential long-term consequences of increases in blood pressure and pulse, a cardiovascular outcomes study was required as a post-approval commitment. This was the genesis of the Sibutramine Cardiovascular Outcomes (SCOUT) trial. Protocol development began in 2000.

In 2002, Italy's Ministry of Health suspended sales of sibutramine due to 50 reports of cardiovascular adverse events, including two deaths. A causal association could not be established and marketing of sibutramine resumed in Italy, but with a reinforcement of the requirement that the cardiovascular outcomes trial be conducted. The trial was initiated in 2002.

Citizens' Petition (2002)

In March 2002, Public Citizen filed a Citizens' Petition requesting the withdrawal of sibutramine from the U.S. market. The petition noted that "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."

In September 2003, Public Citizen provided a supplement to its 2002 petition citing an additional 30 cardiovascular deaths in the FDA AERS database, for a total of 49 cardiovascular deaths. Twenty-seven of the 49 (68%) were in individuals under the age of 50.

In 2005, the Agency responded to the Citizens' Petition. The petition was denied. In the response, it was noted that the Agency's review of AERS revealed 54 domestic reports of death associated with the use of sibutramine. Of those 54 reports, 30 were reportedly due to a cardiovascular cause. But the Agency noted: "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.[1,2,3,4] 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.[5] 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."

The response went on to reference the SCOUT study as the most objective way to assess sibutramine's cardiovascular safety profile when used in obese patients "with known or occult cardiovascular disease."

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[1] Eckel RH, et al. Obesity and heart disease. *Circulation* 1997; 96:3248-3250.
[2] Must A, et al. The disease burden associated with overweight and obesity. *JAMA* 1999; 282:1523-1529.
[3] Manson JE, et al. Body weight and mortality among women. *N Engl J Med* 1999; 333:677-685.
[4] 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.
[5] Rodriquez EM, et al. The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Safe* 2001; 10:407-410.

Despite the denial of the petition, the Agency did undertake a revision to the physician and patient labeling, required the issuance of a *Dear Healthcare Professional* letter, and required an educational outreach program for physicians.

Sibutramine Cardiovascular Outcomes Trial (SCOUT)

SCOUT was a randomized, double-blind, placebo-controlled multicenter trial conducted between January 2003 and March 2009 in Europe, Latin America, and Australia. The study population consisted of approximately 10,000 men and women aged ≥55 with a body mass index (BMI) between 27 kg/m^2 and 45 kg/m^2, or between 25 kg/m^2 and 27 kg/m^2 with an increased waist circumference. Subjects were also required to have a history of cardiovascular disease (coronary artery disease, stroke, occlusive peripheral arterial disease) and/or type 2 diabetes mellitus with at least one other cardiovascular risk factor (i.e., hypertension, dyslipidemia, current smoking, or diabetic nephropathy). All subjects underwent a 6-week lead-in period on sibutramine 10 mg. Eligible subjects were then randomized to either placebo or sibutramine 10 mg daily. Titration to sibutramine 15 mg daily was allowed for individuals with inadequate weight loss on 10 mg daily. The mean duration of exposure to sibutramine and placebo was approximately 3.5 years.

There was a 16% increase in the relative risk of the primary outcome event (POE) (a composite of non-fatal MI, non-fatal stroke, resuscitation after cardiac arrest, and cardiovascular death) in the sibutramine group compared to the placebo group (HR, 1.16; 95% CI, 1.03, 1.31; p=0.02). There was no between-treatment difference in cardiovascular death (HR, 0.99; 95% CI, 0.82 to 1.19; p=0.90) or all-cause mortality (HR, 1.04; 95% CI, 0.91 to 1.20; p=0.54). The primary outcome was driven by non-fatal MI and non-fatal stroke (HR, 1.28; 95% CI, 1.04 to1.57; p=0.02; HR, 1.36; 95% CI, 1.04 to 1.77; p=0.03, respectively).

The difference in mean percent body weight at Month 60 (end of trial) between the sibutramine and placebo groups was approximately 2.5%.

Numerous sub-group analyses were conducted by the sponsor and the Agency to try and identify a population that had a more favorable benefit:risk profile. The sponsor's analyses focused on three defined cardiovascular (CV) risk groups – Type 2 diabetes mellitus (DM) only, CV only, and CV + DM. According to the sponsor's analyses, in the DM-only sub-group there was no difference in risk for any of the CV outcome events or for all-cause mortality between the sibutramine and placebo treatment groups. However, the FDA's analyses revealed that based on the logrank test interaction p-value of 0.56, the treatment effect did not differ significantly among the three CV risk subgroups.

The sponsor and the Agency conducted responder analyses which showed a lower risk of POE in sibutramine responders versus sibutramine non-responders; however, this was also seen in the placebo group, i.e., a lower risk of POE in responders versus non-responders. And when the comparison groups were sibutramine responders versus placebo responders, the sibutramine group had a higher risk of POE than the placebo

group. Similarly, the sibutramine non-responders had a higher risk of POE than the placebo non-responders.

Other pre-specified outcomes of interest included the development of diabetes, atrial fibrillation requiring medication or medical intervention, and obesity-related cancers. The onset of all of the outcomes of interest was similar between treatment groups.

Biomarkers, including adiponectin, leptin, IL-6, TNF-α, and CRP, were evaluated at one investigative site (n=232). The changes in biomarkers were evaluated from baseline to month 12. None of the comparisons of the mean changes in biomarkers between treatment groups were of statistical significance.

Risk Evaluation and Mitigation Strategy

On August 4, 2010, a Medication Guide only REMS was approved for sibutramine, in addition to safety labeling changes which had been submitted as a Changes Being Effected (CBE) supplement on January 29, 2010 and which were the basis of a January 21, 2010 Drug Safety Communication. The safety labeling changes provided for the contraindication of sibutramine in patients with a history of CAD, CHF, tachycardia, peripheral artery occlusive disease, arrhythmia, cerebrovascular disease, inadequately controlled hypertension >145/90, and age >65 years.

The sponsor subsequently submitted a proposed REMS with a Communication Plan, consisting of a *Dear Healthcare Professional* letter, several physician educational and patient monitoring tools, and a restricted dispensing of sibutramine. The key mitigation interventions proposed by the sponsor would include proper patient selection, patient monitoring, and discontinuation of sibutramine in patients who have not responded to therapy after 2 to 3 months.

It was the conclusion of the Office of Surveillance and Epidemiology's Division of Risk Management that the sponsor's proposed REMS would be unlikely to have a large impact on preventing cardiovascular risks associated with sibutramine. One proposed intervention, patient selection to prevent patients with known cardiovascular disease from receiving sibutramine, is being accomplished by the prescribing community already. To identify patients with undiagnosed cardiovascular disease, OSE suggested to the Advisory Committee that a REMS might require a cardiovascular work-up of each patient prior to receiving sibutramine; however, cardiologists on the advisory committee stated that ruling out cardiovascular disease in patients prior to prescribing sibutramine is not feasible. A second intervention proposed by the sponsor, limiting duration of use, would be unlikely to reduce risk because usage data show that most patients do not receive extended courses of sibutramine therapy, and patients can be at increased risk even during short courses of therapy. A third proposed intervention, patient monitoring of blood pressure and heart rate to prevent cardiovascular adverse events, is not supported by the SCOUT data.

A review of the Adverse Events Reporting System (AERS) of spontaneous reports of serious cardiovascular outcomes associated with the use of sibutramine revealed that some patients had asymptomatic and undetected advanced coronary artery disease. Thus, it is unlikely that patients conforming to any intended treatment group identified by simple clinical criteria alone would be reliably free of risk associated with this agent. In considering available options for regulatory action, OSE has concluded that a comprehensive REMS would unlikely mitigate the risks without placing an undue burden on the healthcare system.

Advisory Committee

An Advisory Committee was convened on September 15, 2010, to discuss the SCOUT trial and the continued marketing of sibutramine in the U.S. There was one voting question posed to the committee:

> Based on the information provided in the FDA's and the sponsor's briefing documents and the data presented at the advisory committee meeting, which of the following regulatory actions do you recommend FDA take on sibutramine?
>
> **A.** Allow continued marketing and make no changes to the current labeling.
>
> **B.** Allow continued marketing and revise the current labeling to include a boxed warning about the increased risk for major adverse cardiac events and the need to closely monitor patients' blood pressure and pulse and body weight.
>
> **C.** Allow continued marketing, revise the current labeling to include a boxed warning, and limit use of sibutramine through restricted distribution (e.g., specially trained physicians).
>
> **D.** Withdraw from the U.S. market.

Two members voted for option B; 6 members for option C; and 8 members for option D. A breakdown of the vote by member, as well as a summary of member comments is included in Appendix A.

Conclusion and Recommendation:

Obesity is a chronic disease, the treatment of which is intended to reduce morbidity and mortality. While much attention has been focused on the purported cardiovascular benefit associated with even small amounts of weight loss maintained over several years, this benefit was not supported by the SCOUT trial and in fact, evidence of harm emerged. While the sponsor has suggested that the DM-only group showed a lower risk for POE in the sibutramine group relative to the placebo group throughout the entire study, these findings are at best hypothesis-generating. Given the considerable overlap in patients with obesity, type 2 diabetes mellitus, and cardiovascular disease risk, based on the SCOUT trial it is difficult to tell if there is a point, or population, where the

cardiovascular benefit from weight loss, exceeds the risk from the intrinsic cardiovascular effect of the drug. Even when other potential benefits of weight loss are considered, such as reduction in obstructive sleep apnea, reduction in obesity-related cancers, or prevention of type 2 diabetes mellitus, definitive evidence of benefit has not been shown with the use of sibutramine.

Since there is not a population that has been defined that may benefit from sibutramine, we are not able to develop a risk mitigation strategy.

Therefore, it is the recommendation of the Office of New Drugs and the Office of Surveillance and Epidemiology, that sibutramine should be withdrawn from the U.S. market until or unless data is submitted showing a population that would clearly benefit. The Agency would consider allowing treatment use in limited cases for patients already being treated with sibutramine, for example under an IND protocol, if a strong justification along with a plan to monitor patients could be provided.

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Appendix A:

Vote: **B:** Dennis Dixon, Ph.D.
Mathematical Statistician
NIAID

John M. Flack, M.D., M.P.H.
Professor of Medicine & Physiology
Wayne State University School of Medicine

C: Melanie Coffin
Patient Representative

Peter Gross, M.D.
Executive VP & Chief Medical Officer
Hackensack University Medical Center

Eric Felner, M.D.
Associate Professor of Pediatrics
Emory University School of Medicine

Jodi Segal, M.D., M.P.H.
Associate Professor of Medicine
Johns Hopkins University

Jessica Henderson, Ph.D.
Acting Consumer Representative
Professor of Community Health Education
Western Oregon University

Edward Gregg, Ph.D.
Chief, Epidemiology and Statistics Branch
CDC

D: Katherine Flegal, Ph.D.
Senior Research Scientist
NCHS, CDC

William Hiatt, M.D.
Section of Vascular Medicine
University of Colorado Denver School of Medicine

David Waters, M.D.
Emeritus Professor
Division of Cardiology
University of California San Francisco

Jacqueline Gardner, Ph.D., M.P.H.
Professor Emeritus
Department of Pharmacy
University of Washington

Sanjay Kaul, M.D.
Professor
Division of Cardiology
UCLA

Lamont Weide, M.D., Ph.D.
Chief, Diabetes & Endocrinology
University of Missouri Kansas City

Allison Goldfine, M.D.
Associate Professor
Harvard Medical School

Abraham Thomas, M.D., M.P.H.
Division Head
Endocrinology, Diabetes, Bone, and Mineral Disorders
Henry Ford Hospital

Comments from the committee members:

- Can't identify group where benefit known to outweigh risk
- Don't get other benefits – BP, DM
- Hard to define sub-group to treat
- Biomarkers not improved
- Little use of sibutramine secondary to cost/access
- Limited treatment options – removal would decrease that
- Limited benefit/other benefits not looked at
- Benefit of drug is largely anecdotal
- Vital sign outliers do not predict responders
- Efficacy trial was designed to show benefit. 50% didn't complete. Safety on drug is the better analysis – risk assessed by upper bound of CI
- A lower risk group was studied secondary to the lead-in. Use of lead-in introduced bias. Can't extrapolate results from this trial to a lower risk population.
- Not enough power to look at small sub-groups
- Risk will continue even if marketed to a low risk population
- Nothing to predict optimal benefit:risk
- No data presented to support clear way to mitigate risk
- Need tools to identify at-risk patients
- Risk is not localized to non-responders

- We can’t determine who can be placed on drug safely so how can you say if you do take it, only take it if you lose weight

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/s/

AMY G EGAN
10/07/2010

MARK I AVIGAN
10/07/2010

MARY H PARKS
10/07/2010
signing for Dr. Eric Colman

GERALD J DALPAN
10/07/2010

JOHN K JENKINS
10/08/2010
I concur with the recommendation to ask the sponsor to voluntarily withdraw Meridia from the U.S. market for safety reasons.