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Advisory Committee

Sibutramine Safety: September 15, 2010

(I have no financial conflict of interest)

Basis for Our 2002 Petition to Ban Sibutramine

1/ Pre-approval Clinical Trial Data

2/ Advisory Committee / FDA Medical Officer Concerns

3/ Post Approval AERS reports

Table 1- Percentage of Subjects With Adverse Cardiovascular Reactions in Study BPI 852 (clinical trial before approval—1047 pts)

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

Opinion of FDA Advisory Committee and Medical Officer on Approvability of Sibutramine

- FDA advisory committee (1996) voted five to four that the benefits of sibutramine did not outweigh the risks and also voted 8 to 0 that the pressor (high blood pressure-raising) effect of sibutramine was “clinically important.”

- 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.”

Further Medical Officer Comments

- "sibutramine does not improve, and in some cases it aggravates major obesity-related co-morbidities"

- "5 of the 28 (abnormal sibutramine) ECGs represented clinically significant changes. These changes included frequent ventricular ectopic beats, atrial fibrillation, left bundle branch block, and T wave changes."

  (only 3 abnormal ECGs in placebo group)

Serious Reported AERs by the time of March 2002 Petition to ban Sibutramine

FDA received reports of 29 patient deaths, 19 with 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.

Basis of 2005 FDA Denial of Our Petition to Ban Sibutramine

- “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 was ordered by the EMA)

2005 Annals of Internal Medicine article on Drugs for Obesity by FDA's Dr. Eric Colman

- "Sibutramine…is now the focus of a landmark trial [SCOUT] that is examining, for the first time, whether drug-induced weight loss reduces the risk for fatal and nonfatal cardiovascular disease."

- "Not only is SCOUT a landmark study, it reminds us that there is no substitute for data from large, long-term controlled trials for making the most accurate assessment of a drug's risks and benefits."

- "8 years since the approval of sibutramine, use of the drug remains steady at about 50 000 prescriptions a month, suggesting that the drug has found favor with some dieters;"

(Current monthly sibutramine Rxs (first 6 months of 2010, IMS) are 19,000, a 62 % decrease from 2005, 70% since 2003)

Ann Int Med. Nov 5, 2005

FDA November, 2009 explanation for design of SCOUT

- , ”the [SCOUT] study was designed to show that weight loss with sibutramine and standard care was more effective in reducing the number of cardiovascular events compared to weight loss from a placebo and standard care.”

Basis of Our 12/09 Re-petition to Ban Sibutramine

SCOUT, RCT involving 10,000 obese patients over age 55 with cardiovascular risks, found highly statistically significant increase ($p<.026$) in composite end point (MI, Stroke, resuscitated cardiac arrest or cv death) with sibutramine compared to placebo

By mid-2009, a total of 84 reports of deaths from cardiovascular causes in the FDA Adverse Event Reactions (AERS) database, including 30 in people 50 or younger. Of these 30 people, 11 were 30 or younger.

Basis of 2010 FDA Decision not to Ban Sibutramine

- Have not yet analyzed the data from SCOUT but will strengthen warning label

  (FDA: $p < .023$ for increased composite risk)

- Most patients in SCOUT had label-contraindicated conditions (this despite earlier FDA praise for purpose of SCOUT and importance of study)

- Plan to have an FDA advisory committee

  meeting in the fall of 2010 (8 months after EMA ban)

Basis of 2010 EMEA Decision to Recommend Sibutramine Ban

- "the weight loss achieved with sibutramine treatment is modest in comparison with that obtained with placebo, with patients losing on average two to four kilograms more than with placebo."
- Although contra-indicated in patients with cardiovascular disease… "an increased risk can also apply to [other] patients for whom sibutramine can be prescribed because obese and overweight patients are likely to be at risk of cardiovascular disease."

EMEA Decision (cont'd)

- "Based on the evaluation of the currently available data and the scientific discussion within the Committee…the benefits of sibutramine-containing medicines do not outweigh their risks, and therefore recommended that the marketing authorisations for sibutramine-containing medicines be suspended across the EU. "

Major Findings from SCOUT Study

- 16 % increased risk of primary outcome in subutramine group
- 28% increased risk of non-fatal MI
- 36% increased risk of non-fatal stroke
- No group or subgroup with any evidence of clinical benefit from sibutramine

NEJM, September 2, 2010

U.S. prescriptions for sibutramine since our 2002 petition to ban the drug: health implications

- 3.6 million Rxs (IMS data): 1/03 through 6/10

- If only one out of three of an estimated 600,000 people who have used the drug since 2003 (200,000 people) had the characteristics of the SCOUT population, this would amount to an excess of 73 heart attacks or strokes for every 4900 people (published SCOUT finding) or 2980* extra heart attacks or strokes. This does not even count the other 400, 000 people who may also be at increased risk or the possibility that more than one out of three U.S. users have SCOUT characteristics.

* 200,000/4900 X 73 = 2980

Lessons learned from the sibutramine fiasco

- The 1996 instincts/judgments of the FDA advisory committee and medical officer about increased cardiovascular risk of a drug that increases pulse, blood pressure and arrhythmias were correct.

- The FDA's zeal to replace the recently-banned Redux (the fen of fen-phen) with another weight-reducing drug was dangerous. From Colman's 2005 Annals historical review: "The void created by the withdrawal of dexfenfluramine in September 1997 was quickly filled with sibutramine [approved November 1997]."

British Medical Journal Comment on EMA ban

"The fate of sibutramine reminds us how little antiobesity drugs have had to offer—at best, a reduction of a few per cent in the total burden of excess weight carried until death. With energy homoeostasis so deeply enmeshed in physiology, it has always seemed unlikely that a magic bullet could ever switch off food intake without hitting something vital.."

Prof. Gareth Williams, U. of Bristol; Feb. 9, 2010

Conclusions for the Advisory Committee and FDA

- SCOUT is the first required long-term safety studies for any diet drug. They must be mandated & finished before, not after approval.

- By a larger margin than in 1996, your committee should strongly recommend the ban of sibutramine before more people suffer strokes and heart attacks from a drug without any evidence of clinical benefit. A two to four kilogram weight loss is a deadly trade-off for such increased cardiovascular risks.