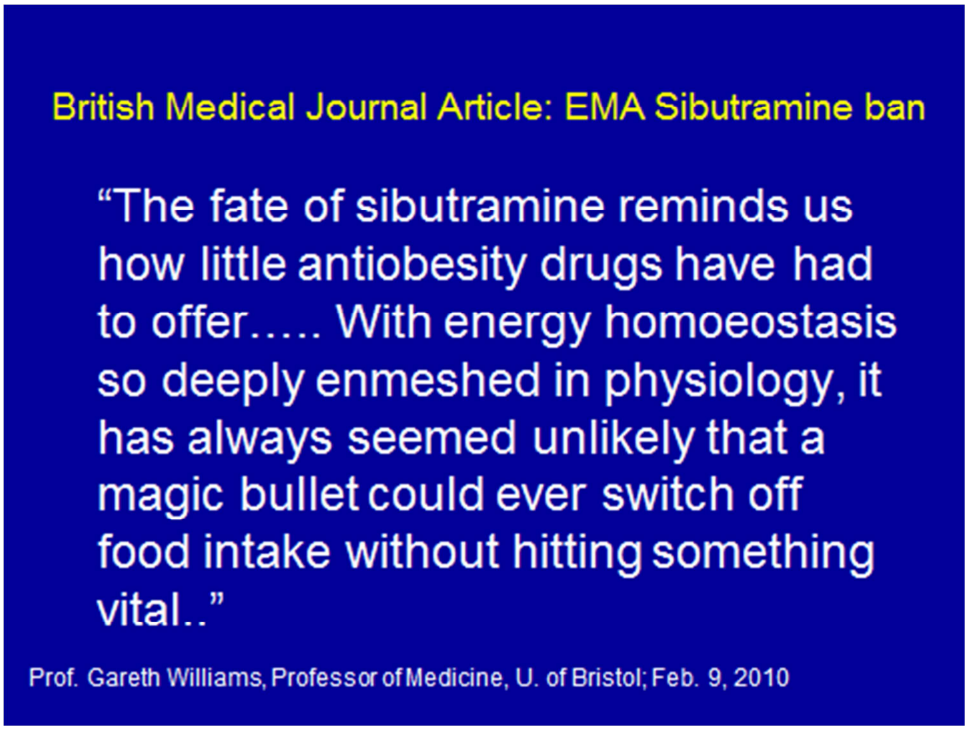
Testimony of Sidney M. Wolfe, M.D., and Sammy Almashat, M.D., M.P.H.

Public Citizen, Health Research Group

Before FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting on Qnexa

February 22, 2012

Shortly after sibutramine (Meridia) was banned in Europe in 2010, an insightful article by endocrinologist Gareth Williams appeared in the *British Medical Journal*:



Phentermine and topiramate, each with different mechanisms for appetite suppression, have a wide scope of pharmacologic sites, beyond the magic-bullet hunger sites. Thus, the variety of adverse effects of Qnexa:

- **Birth defects —** Well documented in both animal studies and human topiramate exposure.

- **Frequent metabolic acidosis —** Usually compensated, but causing increased nephrolithiasis (kidney stones; 22 cases in the Qnexa groups, five in placebo);[1]; the risk of decreased bone mineral density and osteoporosis, not measured in Qnexa

[1] Colman, E. Memo. 15 July 2010, Advisory Committee meeting for phentermine/topiramate (Qnexa). PDF page 5.

trials but suggested by increased bone turnover with topiramate;[2]; and the risk of cardiac arrhythmias.

● **Cognitive effects —** Excess of memory impairment, decreased concentration/ attention. Overall, cognitive-related adverse events occurred in 1.7% of placebo patients and 5.6% of mid-dose Qnexa patients.[3]

● **Cardiovascular risk —** The history of diet drugs is littered with those banned only after serious cardiac risks were documented, after approval.

Phenylpropanolamine PPA (as in Dexatrim) — After case reports of patients with hemorrhagic (bleeding) strokes after using this OTC pill, an epidemiologic study confirmed an excess of such strokes in people using the drug, and it was banned in 2001.

Natural Dexatrim (also OTC) — After its ban, PPA was replaced with **ephedra**, also widely sold as a dietary supplement. We petitioned the FDA in 2001 to ban this ephedra because of increased strokes and heart attacks and it was banned in 2003.

Redux (dexfenfluramine) — Approved in 1996, it was prescribed with a second drug, phentermine, reducing the urge to eat by two different mechanisms. It was quickly discovered that dexfenfluramine caused serious heart valve damage and, as previously suspected, primary pulmonary hypertension. It was banned in 1997, along with fenfluramine.

Meridia (sibutramine) — Approved in 1997. Dr. Eric Colman was the FDA physician and primary reviewer for the drug who, with a narrow majority of the 1996 version of your committee, opposed its marketing because of pre-approval evidence of increased cardiovascular risk. Colman later wrote, “The void created by the withdrawal of dexfenfluramine in September 1997 was quickly filled with sibutramine [approved November 1997].”[4] The drug was taken off the market in Europe in 2010, later that year in the U.S., when a large, 10,000-person randomized trial (SCOUT) found a significant increase in strokes (36%) and heart attacks (28%) with sibutramine compared to placebo. In this article, Colman also stated “ SCOUT … reminds us that there is no substitute for data from large,

[2] Epilepsia. Heo, et al. 2011Oct;52 (10); 1884-9.
[3] Current FDA Briefing Document, page 4.
[4] Ann Intern Med. 2005 Sep 6;143(5):380-5. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. Colman E.

long-term controlled trials for making the most accurate assessment of a drug's risks and benefits."

Qnexa (phentermine and topiramate)

The following findings from randomized studies are of concern because they signal increased cardiovascular risk:

1/ Increased pulse rate with Qnexa, including an excess of greater than 20 bpm increases. The timing of pulse measurement affected the Qnexa pulse rate, according to the FDA. "Overnight ... measurements of heart rate showed a reduction… in both placebo and PHEN/TPM groups" but "daytime heart rate measurements demonstrated a mean increase of 6 bpm over placebo with high-dose [Qnexa]."[5] The immediate release of phentermine occurs in the morning, and higher daytime heart rate could be partially on this basis. Several studies have found that increased pulse rate is an independent risk factor for cardiovascular disease.[6]

2/ Increased arrhythmias in Qnexa patients. In the high-dose group, arrhythmia-related adverse events occurred at an incidence of 4.7% compared to 1.8% for placebo.[7] Some cases were tachycardia, but there were also four cases of treatment-emergent atrial fibrillation, two of ventricular extrasystole, and one of supraventricular extrasystole in the Qnexa patients (2,318 patients), with just two cases of atrial fibrillation and one of ventricular extrasystole in the placebo group (1,561 patients).[8] There is some evidence that metabolic acidosis can be a risk factor for cardiac arrhythmias.

3/ All four nonfatal myocardial infarctions were in Qnexa patients; there were none in placebo patients.[9] (A fifth Qnexa MI was recorded in the second-year follow-up (OB-305); there were none in the placebo group.[10])

Discomfort about Qnexa risks expressed by advisory committee members at the 2010 meeting includes the following[11]:

A. "I'm also equally concerned about the erosion of the public's trust every time we approve a drug and don't get it right the first time, either because the

[5] Current FDA Briefing document, page 110.
[6] Palatini P. Elevated heart rate: a "new "cardiovascular risk factor? Prog Cardiovasc Dis 2009;52:1-5.
[7] Colman, E. Memo. 15 July 2010, Advisory Committee meeting for phentermine/topiramate (Qnexa). PDF page 6
[8] Vivus current briefing document, Table 42, page 119.
[9] Clinical Briefing Document 7/15/10 Endocrine and Metabolic Drugs Advisory Committee Meeting, p. 99
[10] Vivus current briefing document, Table A5.1, page 41-3.
[11] Transcript of 7/15/10 Advisory Committee meeting.
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm

sponsors have not done due diligence and looked for that signal in the right population ... or ... sample size is not large enough for the signal to be captured."

B. "The concerns we have are with safety. And as previously mentioned, we want to make sure we avoid a situation where, five years from now, we're back for an advisory meeting considering safety."

C. "I would agree, I am really sick of taking medicines off of the market after they've been on a year or two because we've identified something that we didn't know about."

The most important new information since 2010 was the SCOUT study, with its implications for Qnexa. As the only large, long-term diet drug RCT ever done, the findings of significantly increased cardiovascular risk, consistent with pre-approval risk findings, are quite relevant for Qnexa.

Public health cannot tolerate yet another drug approval for a diet drug not accurately assessed for cardiovascular risks, especially in light of suggestive findings of such risks with Qnexa. The danger of another approved diet drug hitting "something vital" — the cardiovascular system — is no longer acceptable when it could be prevented by a large clinical trial powered to evaluate such risk prior to approval.

We urge a yes vote for question 4: "Discuss whether you believe the available data for PHEN/TPM warrant that a cardiovascular outcomes trial be conducted prior to approval."