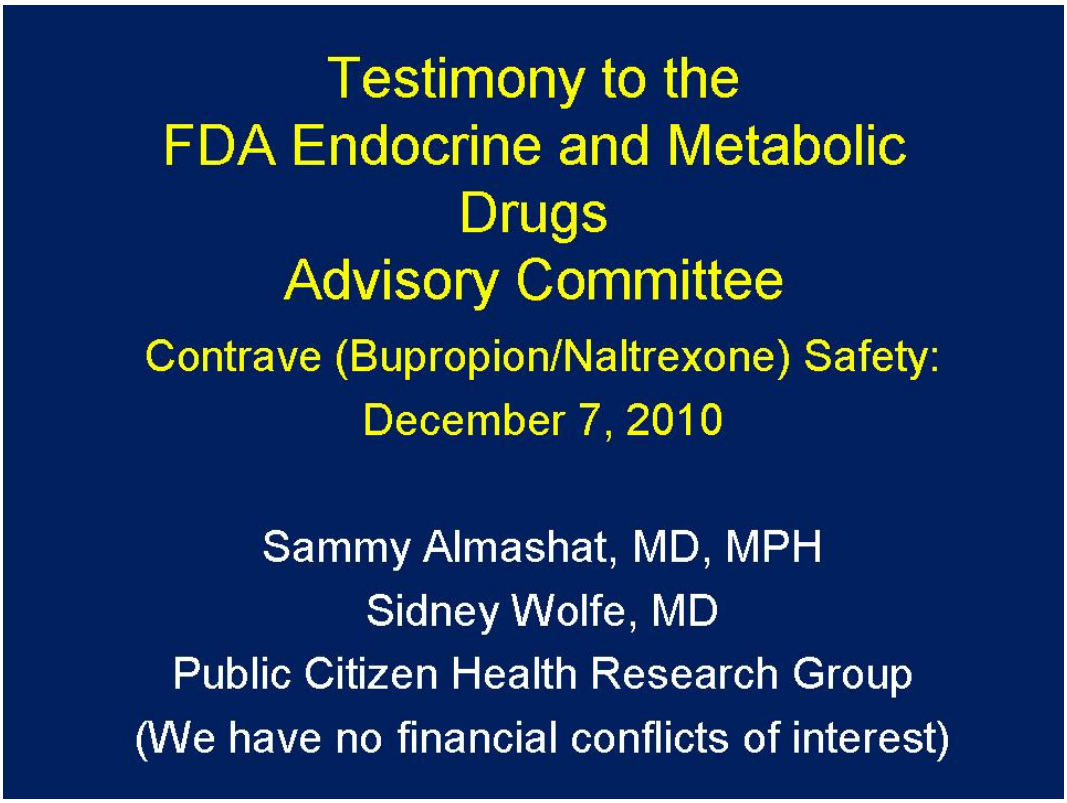
Testimony on Contrave (Bupropion/Naltrexone) Safety

December 7, 2010

Before the FDA Endocrine and Metabolic Drugs Advisory Committee
Testimony of Sammy Almashat, M.D., M.P.H. and Sidney Wolfe, M.D.
Public Citizen Health Research Group



Contrave is the latest in a long line of weight loss drugs. All of the 7 drugs below, once approved for weight reduction, had severe cardiovascular side effects and were banned or delisted for weight loss.

Drug	Year Approved	Year Taken Off Market	Serious Adverse Effects
Thyroid Hormone	1893	1949	Hyperthyroidism (which includes cardiac effects)[1]
Amphetamine	1937	1971	Known cardiovascular toxicity
Aminorex	1967	1972	Pulmonary Hypertension[2]
Fenfluramine	1973	1997	Heart Valve Insufficiency and Primary Pulmonary Hypertension[3,4]
Phenylpropanolamine	1960	2000	Hemorrhagic Stroke[1]
Ephedra	n/a	2004	Heart Attack and Stroke[5]
Sibutramine	1997	2010	Heart Attack and Stroke[6]

1 Astrup A. Is cardiometabolic risk improved by weight-loss drugs? Lancet. 2010 Aug 21;376(9741):567-8. Epub 2010 Jul 29. 2 Fishman AP. Aminorex to Fen/Phen: An Epidemic Foretold. Circulation. 1999;99:156-161. Web. Accessed on December 6, 2010. http://circ.ahajournals.org/cgi/content/full/99/1/156 3 FDA. Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux), 9/18/1997 (updated: 7/7/2005) Web. Accessed on December 6, 2010. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm 4 Br Heart J. 1993 Dec;70(6):537-41. Primary pulmonary hypertension and fenfluramine use. Brenot F, Herve P, Petitpretz P, Parent F, Duroux P, Simonneau G. 5 FDA Press Release, Feb. 6, 2004. FDA Issues Regulation Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids and Reiterates Its Advice That Consumers Stop Using These Products. Web. Accessed on December 6, 2010. http://web.archive.org/web/20080223161240/www.fda.gov/bbs/topics/NEWS/2004/NEW01021.html

6 James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, Torp-Pedersen C, Sharma AM, Shepherd GM, Rode RA, Renz CL; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010 Sep 2;363(10):905-17.

Bupropion: Adverse Effects

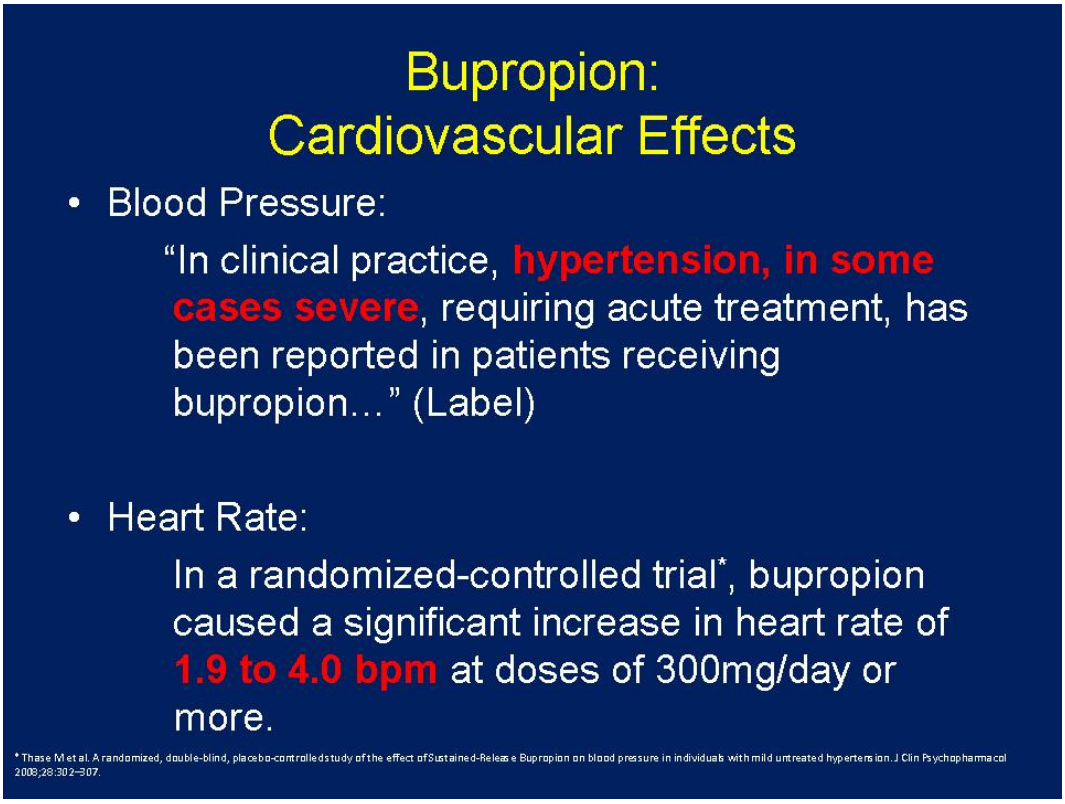
Bupropion: Seizures

The recommended daily maintenance dose of Contrave contains 360mg of bupropion. The incidence of seizures for bupropion alone is estimated to be 4 per 1,000.*

With millions of new people likely to receive this drug, if approved, this could represent an enormous burden of new disease.

(Two seizures occurred in Contrave patients, none in patients getting a placebo)

* Johnston JA, Lineberry CG, Ascher JA, Davidson J, Khayrallah MA, Feighner JP, Stark P. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry. 1991 Nov;52(11):450-6.



Bupropion has documented effects on blood pressure and heart rate. As the Label points out…

Contrave (NB): Adverse Effects

Contrave: Renal Effects

Table 1. Shifts to high creatinine in Phase III Trials (percent shifting from normal to >/= upper limits of normal levels)

	Placebo	Total NB (Contrave)
Total	1.9%	7.6%
Diabetic	3.1%	12.7%
Non-diabetic	1.7%	7.0%

Patients on Contrave in clinical trials were 4x more likely to have a shift to high creatinine levels relative to placebo. This was the case in both non-diabetic and diabetic patients, the latter already at increased risk of renal disease.

According to JNC-7,*:

"the relationship between BP and risk of CVD events is **continuous**, consistent, and independent of other risk factors"

and:

"**even modest increases** in blood pressure and pulse are associated with an elevated risk of cardiovascular events"

*JNC7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf (p 79, FDA Clinical Briefing Document)

Percentage of Subjects With Adverse Cardiovascular Reactions With Contrave (NB32)

Adverse Event	NB32	Placebo
Systolic HBP	6.7%	3.9%
Rapid Heart Rate	1.1%	0.5%
Palpitations	2.2%	0.9%

Contrave caused higher rates of elevated systolic blood pressure, rapid heart rate and palpitations in the Phase III trials.

Percentage of Subjects With Adverse Cardiovascular Reactions in Study BPI 852 (clinical trial before approval)		
Adverse Event	Sibutramine	Placebo
High Blood Pressure	2.1%	0.8%
Rapid Heart Rate	2.8%	0.5%
Palpitations	3.1%	1.2%

Similarly, prior to approval, Sibutramine had the same three increases in these cardiovascular risk factors. These were the reasons that both the Medical Officer and Advisory Committee were opposed to approving the drug at the time.

Treatment-emergent dropouts/reasons leading to discontinuation (all significant)

Adverse Event	Placebo (1515)	Total NB (3239)	P-value
Subjects Discontinuing Treatment due to any AE	181	771	<0.001
Hypertension	0	11	0.021
Palpitations	0	10	0.031
Nausea	3	203	<0.001
Vomiting	1	35	<0.001
Dizziness	5	42	0.001
Headache	9	55	0.002

Hypertension or palpitations were severe enough to cause 21 Contrave patients to withdraw from the trial; no patients taking placebo withdrew for these reasons. Unfortunately, the following patient was not withdrawn from the study despite persistent hypertension and died from a myocardial infarction.

P76, FDA Briefing Document: Table 29: Treatment-Emergent Adverse Events (≥0.5% in Any Group) Leading to Treatment Discontinuation: Primary Dataset, Double-Blind Treatment Phase

Patient Death from Fatal Myocardial Infarction in Clinical Trial

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Table 26: Blood Pressure and Pulse Rates by Visit for Subject 099-NB-301-003

Visit	Blood Pressure (mm Hg)	Pulse (beats per minute)
Screening	137/79	43
Baseline	139/83	43
Week 4	135/78	50
Week 8	148/82*	57
Week 12	133/79	55
Week 16	133/77	47
Week 20	142/76*	43
Week 24	134/77	49
Week 28	156/82*	47
Week 32	136/75	49
Week 36	165/80*	41
Week 40	152/78*	41
Week 44	150/78*	43

*highlighted blood pressures are hypertensive readings per JNC7

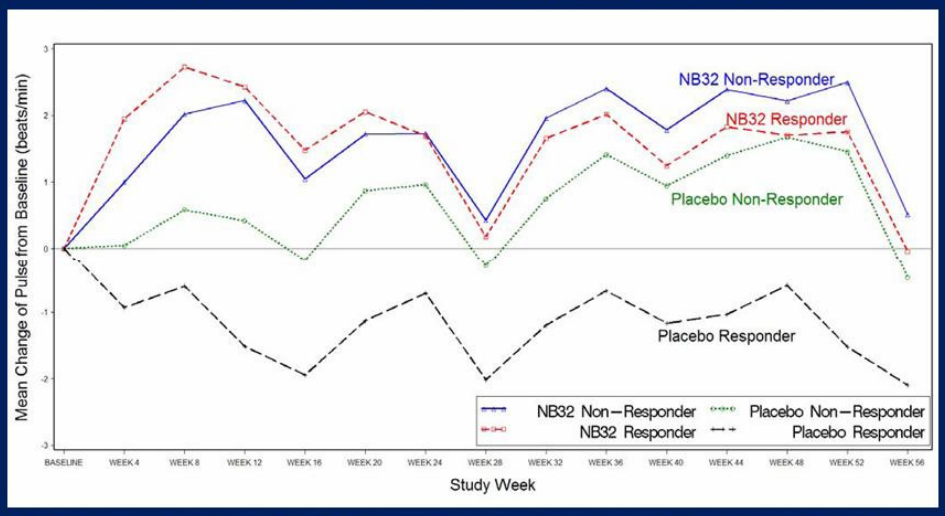
Shortly after a study visit on Day 312 (Week 44), the subject's wife informed the study site that the subject had experienced chest pain, and that he had made an appointment to see his primary care physician. On Day 324, the subject experienced a fatal myocardial infarction during a camping trip at a remote location.

*Reviewer comment (p72 – FDA clinical briefing documents): …**it is concerning that his systolic blood pressure increased despite significant weight loss.***

This was one of 3 myocardial infarctions in those receiving Contrave. In this case, the

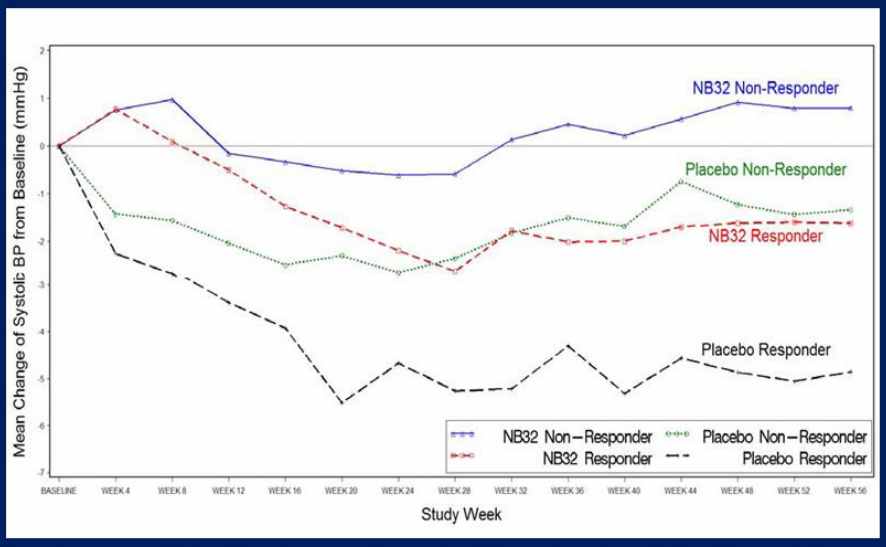
FDA Reviewer noted that "…it is concerning that his systolic blood pressure increased despite significant weight loss".

Contrave Nullifies the Beneficial Effects of Weight Loss on Heart Rate



The previous patient is representative of the central issue in today's hearing: Diet pills, like Meridia and Contrave, have been repeatedly shown to nullify the beneficial effects of weight loss on cardiovascular markers for disease. Here, even though the Contrave (NB32) responders lost more weight than those on placebo, the benefits of the weight loss on heart rate were more than nullified by the drug.

Contrave Largely Nullifies the Beneficial Effect of Weight Loss on Blood Pressure



The same problem is seen with systolic blood pressure. Any benefit of weight loss on this critical marker of cardiovascular health is largely eliminated by Contrave (NB32).

The worsening of key cardiovascular risk factors of blood pressure, heart rate and palpitations caused by Contrave nullifies the cardiovascular benefit of weight loss in these patients.

To increase the cardiovascular risk to these patients, who are already vulnerable to cardiovascular disease, is unacceptable.

After the ban of Sibutramine in the UK, an editorial stated that…