Summary Minutes of the
Endocrinologic and Metabolic Drugs Advisory Committee
The FDA White Oak Campus
Building 31, the Great Room (1503)
Silver Spring, Maryland
December 7, 2010

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the December 7, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on Jan. 25, 2011

I certify that I attended the December 7, 2010 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Paul T. Tran, R.Ph
Designated Federal Official, EMDAC

/s/
Abraham Thomas, M.D., M.P.H.
Committee Acting Chair

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research met on December 7, 2010 at The FDA White Oak Campus, Building 31, the Great Room, Silver Spring, Maryland. Prior to the meeting, members and invited consultants had been provided the background material from the FDA and Orexigen Therapeutics, Inc. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Official). There were approximately 250 persons in attendance. There were nine speakers for the Open Public Hearing session.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Eric Felner, M.D., Allison Goldfine, M.D., Abraham Thomas, M.D. (Acting Chair), M.P.H., Lamont Weide, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members NOT Present:
Thomas Bersot, M.D., Ph.D., David Capuzzi, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-voting):
Enrico Veltri, M.D. (Industry Representative)

Temporary Voting Members (Voting):
Marshall Balish, M.D., Vera Bittner, M.D., Melanie Coffin *(Patient Representative)*, John Flack, M.D., M.P.H., Jacqueline Gardner, Ph.D., M.P.H., Susan Heckbert, M.D., Ph.D., Ed Hendricks, M.D., William Hiatt, M.D., Jules Hirsch, M.D. (by telephone), Sanjay Kaul, M.D., Elaine Morrato, Dr.P.H., M.P.H., C.P.H., David Oakes, Ph.D., Michael Proschan, Ph.D., Michael Rogawski, M.D., Ph.D., Ellen Seely, M.D., Ida Spruill, Ph.D., R.N. *(Acting Consumer Representative.)*

FDA Participants (Non-voting):
Eric Colman, M.D., Eileen Craig, M.D., Curtis Rosebraugh, M.D., M.P.H.

Open Public Hearing Speakers:
Morgan Downey, J.D., Obesity Policy Consultant, Publisher & Editor, The Downey Obesity Report
Domenica Rubino, M.D., Director, Washington Center for Weight Management & Research
Kelly L. Close, President, Close Concerns
Joe Nadglowski, Jr., President, Obesity Action Coalition (OAC)
Jennifer Lovejoy, Ph.D., speaking on behalf of the Obesity Society
Kate Ryan, M.P.A., Program Coordinator, National Women's Health Network
Sharon Oxx

Ted Kyle, R.Ph, M.B.A., ConscienHealth
Diana Zuckerman, Ph.D., President, National Research Center for Women & Families, Cancer Prevention and Treatment Fund

Designated Federal Official:
Paul Tran, R.Ph.

Issue:

The committee met and discussed the safety and efficacy of new drug application (NDA) 20–0063, proposed tradename CONTRAVE (naltrexone HCl/bupropion HCl) extended release tablets, manufactured by Orexigen Therapeutics, Inc., for the treatment of obesity and weight management, including weight loss and maintenance of weight loss in patients with an initial body mass index (BMI) of equal to or greater than 30 kilograms (kg) per square meter, or a BMI equal to or greater than 27 kg per square meter with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension).

Call to Order and Introductions	**Abraham Thomas, M.D., M.P.H.** *Acting Chair* Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)
Conflict of Interest Statement	**Paul Tran, R.Ph.** Designated Federal Official, EMDAC
Introduction/Background	**Eric Colman, M.D.** Deputy Director Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation (ODE) II Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER) FDA
SPONSOR PRESENTATION	**Orexigen Therapeutics, Inc.**
Introduction	**Dawn Viveash, M.D.** Senior Vice President Head, Regulatory Affairs & Safety Orexigen Therapeutics, Inc.
Obesity: Clinical Perspective	**Caroline Apovian, M.D., FACP, FACN** Director, Nutrition and Weight Management Center at Boston Medical Center Director, Clinical Research at the Obesity Research Center of Boston Medical Center
Efficacy	**Eduardo Dunayevich, M.D.** Chief Medical Officer Orexigen Therapeutics, Inc.
Safety	**Preston Klassen, M.D., M.S.H.**

	Senior Vice President Head of Global Development Orexigen Therapeutics, Inc.
Risk Mitigation	**Dawn Viveash, M.D.** Senior Vice President Head, Regulatory Affairs & Safety Orexigen Therapeutics, Inc.
Benefit/Risk	**John Buse, M.D., Ph.D.** Professor of Medicine Director, Diabetes Care Center Chief, Division of Endocrinology Executive Associate Dean for Clinical Research University of North Carolina School of Medicine
Closing Remarks	**Preston Klassen, M.D., M.S.H.** Senior Vice President Head of Global Development Orexigen Therapeutics, Inc.
Clarifying Questions from the Committee to Sponsor	
BREAK	
FDA PRESENTATION	
FDA Clinical Review of Efficacy and Safety NDA 200063 naltrexone/bupropion	**Eileen Craig, M.D.** Primary Reviewer DMEP,ODE II OND, CDER, FDA
Clarifying Questions from the Committee to FDA	
LUNCH	
Open Public Hearing Session	
Questions from Committee to Sponsor and FDA	
BREAK	
Discussion/Questions to the Committee	
ADJOURNMENT	

Questions to the Advisory Committee:

Taking into account the material provided in the background documents and presented at the advisory committee meeting, please comment on whether you believe that the sponsor has:

1. Provided adequate evidence to establish naltrexone/bupropion's efficacy as a weight-loss drug? Are there additional studies that you would recommend pre- or post-approval to further evaluate naltrexone/bupropion's efficacy?

The committee agreed that the sponsor did not meet the first criterion which required individuals taking the product to loose 5% or more of their body weight compared to the placebo group. The committee agreed that the sponsor did meet the second criterion. The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.
There was agreement from the committee that further studies are needed to evaluate efficacy, the committee specifically noted that a study on a broader population is needed and such a study should also be representative of higher risk populations and minorities. The committee noted that there was a large amount of missing data due to several factors including the particularly high dropout rate among patients in the study. The committee also noted that efficacy may have been overestimated, thus more reasonable measures of outcome are needed.

2. Adequately assessed and characterized the potential risk for psychiatric and cognitive-related adverse events such as suicidality, sleep disorders, and memory impairment?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

    The committee generally agreed that more data is needed to characterize the potential for cognitive and psychiatric-related adverse events. The 46% dropout rate amongst patients in the study was highlighted as a barrier to the adequate evaluation of these risks. There was a concern about related effects such as dizziness and anxiety as well as effects the potential for suicidal ideation. The committee concluded that there is a need for further study regarding such effects.

    The committee noted that the use of real-time data gathering in the post-marketing setting would be useful for evaluating safety and efficacy. In particular, they stressed the need to evaluate the effects of the use of

naltrexone/bupropion in combination with other psychoactive medications. While the current labeling for the product does not address this, the potential for off-label use should be taken into account. Because the labeling for this product does not mention these details, the committee recommended they be included in labeling.

3. Adequately assessed and characterized the potential for seizures?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

    The committee commented on the current Risk Evaluation Mitigation Strategy (REMS), expressing concern over its success in evaluating the risk for seizures. The committee noted that because bupropion is currently approved for other indications including smoking cessation, evaluation of risk this drug is attainable, however, the risk is combination with naltrexone remains largely unknown. The committee felt that more data regarding risk for seizures is strongly needed.

4. Adequately assessed and characterized the potential clinical significance of increases in serum creatinine?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

    The committee concluded that the sponsor was very receptive in performing further studies involving serum creatinine increases associated with naltrexone/bupropion. An observed decline in renal functioning was highlighted as a needed focus point for future investigation. The committee expressed concern regarding the serum creatinine effects of naltrexone/buproprion in association with other medications. NSAIDs were mentioned as a category of medications needing to be evaluated, as they are often used by obese patients with joint disease. The committee concluded that further studies are needed to evaluate whether or not the observed increases in creatinine) levels are meaningful in the clinical setting.

5. Adequately assessed and characterized the effect of naltrexone/bupropion on blood pressure and pulse?

a. Are there additional studies that you would recommend pre- or post approval to further characterize naltrexone/bupropion's effect on blood pressure and pulse?

b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

The committee felt that while the sponsor did adequately characterize the effects of the product on blood pressure and pulse, current data is not sufficient to evaluate these risks in a larger population. The committee stressed the need to study these effects in high risk populations, specifically those inclusive of individuals with cardiovascular and coronary artery disease risk factors. The committee expressed an appreciation for a larger trial that is planned but commented on the importance of this trial not being delayed.

The committee also stated that there is a need to further evaluate labeling, mentioning that the current labeling does not state when patients should discontinue the use of the naltrexone/bupropion product; noting that on the other hand, appropriate threshold values may be hard to establish. Additionally, the committee felt there may be a need for frequent physician follow-up to monitor the effects of the naltrexone/bupropion combination, given its known effect on blood pressure and pulse.

6. Taking into account naltrexone/bupropion's effect on blood pressure and pulse, please vote whether you believe that a controlled clinical trial adequately designed to examine the drug's effect on risk for major adverse cardiac events should be conducted:

VOTE: **A**. Prior to approval **B**. As a post-approval requirement

A: 8 **B: 11** **Abstain: 1**

Many members struggled with their votes for pre or post-approval requirement. Several members indicated that it would not be appropriate to change the requirement midstream and believed the sponsor did a good job in adhering to guidelines set forward by the FDA Guidance to Industry. Members would like to see the protocol concept agreed upon with the FDA and a timeline for implementation and the milestones be clearly set. The FDA should use its regulatory authority to ensure that planned safety trials are followed through adequately. Several members recommended that the agency should make a contingency at the start of this trial to obtain some interim data before it can consider approval. Several members also felt that an observational study not be sufficient and recommended a randomized clinical trials be performed instead.

7. Taking into account the information provided in the background documents, the presentations made at this advisory committee meeting, please vote whether you believe that the available data adequately demonstrate that the potential benefits of naltrexone/bupropion outweigh the potential risks when used long-term in a population of overweight and obese individuals?

   VOTE: Yes: 13 No: 7 Abstain: 0

   a. If voting 'Yes' please provide your rationale and comment on the need for and approach to post-approval risk management.

   b. If voting 'No' please provide your rationale and comment on what additional clinical would be required to potentially support approval.

Although the sponsor met agency requirements for efficacy, members commented that they would like to have seen greater efficacy with this drug combination. Several members agreed that there is potential for this drug to benefit very specific patient populations population, thus approval should be granted with provisions for a larger study. The committee noted, as stated previously, that it is incumbent upon the FDA to ensure that risk for seizure is appropriately communicated in product labeling. Additionally, there should be clear warnings for use in elderly patients and patients with a history of depression. Members voting not to approve indicated that data simply did not demonstrate that benefits from this drug did not outweigh the potential risk, as they felt efficacy was marginally demonstrated.

Please see transcripts for detailed discussion.