# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 200063Orig1s000

# OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

**COMPLETE RESPONSE**

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Sr. VP, Global Regulatory Affairs
3344 North Torrey Pines Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) dated March 31, 2010, received March 31, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8mg/90mg.

We acknowledge receipt of your amendments dated May 4, 14, and 24, June 11 and 21, July 2, 9, 12, 21, and 29, August 26, September 8 and 17, October 8, November 19, and December 1 and 30, 2010, and January 21, 2011.

We also acknowledge receipt of your amendment dated January 27, 2011, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. Below we describe the reasons that led to this action and provide our recommendation to address the deficiency.

## APPROVAL DEFICIENCY

In general, in your phase 3 clinical trials, mean systolic and diastolic blood pressure and heart rate were statistically significantly higher in naltrexone/bupropion-treated subjects compared with placebo-treated subjects. In addition, there were more adverse events related to hypertension in the naltrexone/bupropion groups, particularly in subjects with type 2 diabetes. These findings raise concern about the cardiovascular safety profile of naltrexone/bupropion when used long-term in a population of overweight and obese subjects.

Therefore, before your application can be approved, you must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

## LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submissions dated March 31, 2010, and January 21, 2011, which contains a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride), if it is approved, to ensure that the benefits of the drug outweigh the risks of seizure-related adverse events and suicidal thoughts or behaviors. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT for NDA 200063**." If you do not submit electronically, please send 5 copies of your REMS-related submissions.

## SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

**POSTMARKETING REQUIREMENTS UNDER 505(o)(3)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

In clinical trials, patients treated with CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) experienced an increase in serum creatinine levels. As a result, an *in-vitro* drug-drug interaction (DDI) study was conducted to evaluate whether naltrexone, bupropion, and their respective metabolites inhibit Organic Cation Transporter 2 (OCT2), which is involved in the tubular secretion of creatinine. The *in-vitro* study results showed that bupropion and its metabolites inhibit OCT2, and suggest that the increase in serum creatinine could be due to the OCT2 inhibition. However, this finding alone does not establish that the increase in serum creatinine is not due to CONTRAVE's (naltrexone hydrochloride/bupropion hydrochloride) effect on the glomerular filtration rate. Thus, this issue requires further evaluation.

Based on the above, FDA has determined that if NDA 200063 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of compromised renal function.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this potential serious risk.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 200063 is approved, you will be required to conduct the following:

1. An *in-vivo* drug-drug interaction study evaluating the impact of CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets on an OCT2 substrate such as metformin hydrochloride.

## NONAPPROVABILITY ISSUES AND RECOMMENDATIONS

We have the following recommendations which are not approvability issues, but we would like you to respond to them when you submit your complete response.

### Biopharmaceutics

1. Based on the information provided, your choice of dissolution method is acceptable. However, your proposed dissolution specifications are not acceptable. Based on the dissolution results from the stability batches, the following table describes our recommendation for your proposed 8 mg/90 mg naltrexone hydrochloride and bupropion hydrochloride product with a side-by-side comparison to your proposed specifications:

| **Actives** | **Time (Hr)** | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 | 1 | 2 | 3 | 4 | 6 |
| | **Sponsor's Proposed Specifications** | | | | | |
| **Naltrexone HCl** | (b) (4) | | | | | |
| **Bupropion HCl** | | | | | | |
| | **Agency's Recommended Specifications** | | | | | |
| **Naltrexone HCl** | (b) (4) | | | | | |
| **Bupropion HCl** | | | | | | |

2. Your evaluation of the effect of alcohol (ethanol) on the *in-vitro* dissolution of bupropion hydrochloride or naltrexone hydrochloride, as submitted in this application, is deficient. You did not investigate testing in 0.1 N HCl (pH 1.2) containing a range of alcohol concentrations to evaluate potential for *in-vivo* dose dumping in presence of ethanol. Provide these data as soon as they are available.

### Statistics

3. You have proposed an algorithm for the early identification of subjects who may not benefit from Contrave because of insufficient weight loss and/or an unacceptable increase in blood pressure. We recommend that you revise this algorithm as described below. We recommend that you provide your plan for comment prior to submission in your complete response. Our recommendations for developing the statistical aspects of this algorithm and for submitting this information for further review are as follows:

   a. Obtain concurrence from us regarding the criteria for the clinical importance of blood pressure changes and weight changes and the time frame for evaluation.

b. Based on the agreed-upon criteria, we recommend that you develop the statistical aspects of the patient management algorithm as follows:

- Obtain and evaluate prediction equations for each Phase 3 study separately.
- For each study, use the intention-to-treat population, with non-responder imputation for subjects who discontinued study medication prior to the week at which the predictive value of early weight loss or early blood pressure changes are to be evaluated.
- Assess whether results from each study are similar enough to be combined; interpret any substantial differences among studies.
- If study results can be combined, obtain combined prediction equations for weight loss and blood pressure changes. Develop a patient management algorithm based on the combined prediction equations.
- Submit the proposed patient management algorithm and the analytical results to support the algorithm for review prior to submission of your complete response.

**Clinical**

4. The patient reported outcome (PRO) dossier submitted does not provide adequate documentation of content validity for the Impact of Weight on Quality of Life (IWQOL-Lite) instrument. The adequacy of the qualitative research used to generate the items and test their clarity, comprehensiveness, and relevance could not be assessed. For instance, patients who were interviewed for concept elicitation were all enrolled in a quasi-residential multidisciplinary treatment program; these patients might not be representative of the clinical trial population. No data were available regarding the socio-demographic and medical status of the patients involved in this qualitative research. You have not submitted qualitative protocols, interview guides, transcripts or the publications supporting this research for our review.

In addition, we have the following concerns on reviewing the instrument items and domains.

a. Many items of the IWQOL-Lite subscales (Self-esteem, Sexual Life, Public Distress, and Work) represent concepts that result from the impact of obesity/weight problems but are also a result of the impact of many other factors in life.

b. The response options (“never true” to “always true”) for the IWQOL-Lite scales require that the patients rate their level of agreement with certain difficulties they might be experiencing due to their weight. These response options do not allow for a direct measurement of a symptom frequency, severity, duration, or interference or reduced physical functioning. Data collected through this scale are therefore difficult to interpret. For instance, how can we quantify a treatment benefit for a patient who had indicated

that at baseline it was "sometimes true that because of his or her weight she or he is afraid of being rejected" while at week 52 it is "rarely true that because of his or her weight she or he is afraid of being rejected"?

c. Each of the items requires that patients assign attribution to the particular symptom or impact. It is not always possible for patients to do this. For example, it may not be reasonable to require patients to ascribe their low sexual desire to their weight when this may be related to a multitude of factors.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research

ENCLOSURE:
APPENDIX A: REMS TEMPLATE
APPENDIX B: SUPPORTING DOCUMENT

**Initial REMS Approval: XX/XXXX**
**Most Recent Modification: XX/XXXX**

## APPENDIX A: REMS TEMPLATE

*If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.*

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

## RISK EVALUATION AND MITIGATION STRATEGY (REMS)

### I. GOAL(S):

List the goals and objectives of the REMS.

### II. REMS ELEMENTS:

#### A. Medication Guide or PPI

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

#### B. Communication Plan

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

#### C. Elements To Assure Safe Use

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:*

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

### D. Implementation System

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

### E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7$^{th}$ year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

**APPENDIX B: SUPPORTING DOCUMENT**

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ERIC C COLMAN
01/31/2011