DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

NDA APPROVAL

Orexigen Therapeutics, Inc.
Attention: Teri Johnson, RAC
Senior Director, Regulatory Affairs
3344 North Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Ms. Johnson:

Please refer to your New Drug Application (NDA) dated and received March 31, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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 and 12, November 19, and December 1 and 30, 2010, and January 21 and 27, 2011, December 10 and 27, 2013, and January 27, February 7, March 3, April 16, May 30, August 1, and September 2 and 8, 2014.

The December 10, 2013, submission constituted a complete response to our January 31, 2011, action letter.

This new drug application provides for the use of Contrave (naltrexone hydrochloride/ bupropion hydrochloride) extended-release tablets, 8mg/90mg, as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related co-morbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on August 1 and September 8, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 200063**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 6 years (inclusive) because necessary studies are impossible or highly impracticable. This is because weight maintenance, not weight loss, is the clinical goal for obese children 2 to 6 years of age. Weight loss is not recommended in children less than 2 years of age because of the requirement for adequate growth and development and optimal deposition of lipids in the developing nervous system.

We are deferring submission of your pediatric studies for ages 7 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2778-1 A juvenile animal study with the combination of bupropion and naltrexone to assess post-natal growth and development with additional assessment of behavior, learning and memory.

Final Protocol Submission:	July 2015
Study/Trial Completion:	December 2016
Final Report Submission:	March 2017

2778-2 A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 12-17 years (inclusive). Part B should not be initiated until after the data from the juvenile animal study (PMR 2778-1) have been submitted to and reviewed by the Agency.

Final Protocol Submission:	December 2015
Study Completion:	May 2020
Final Report Submission:	November 2020

2778-3 A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 7-11 years (inclusive). Part B should not be initiated until the results of the adolescent pharmacokinetics, safety, and efficacy study (PMR 2778-2) have been submitted to and reviewed by the Agency.

Final Protocol Submission:	December 2020
Study Completion:	December 2023
Final Report Submission:	June 2024

Submit the protocols to your IND 068858, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC**

ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Identify an unexpected serious risk of QT prolongation with Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended-release tablets.
- Assess signals of a serious risk of major adverse cardiovascular events (MACE) with Contrave. There have been signals of a serious risk of MACE with some medications developed for the treatment of obesity, and available data have not definitively excluded the potential for this serious risk with Contrave.
- Identify an unexpected risk of increased or more severe serious adverse events in patients with renal and/or hepatic impairment treated with Contrave, due to altered kinetics of the drug in these patients.
- Identify an unexpected risk of increased or more severe serious adverse events in patients taking Contrave and an organic cation transporter 2 (OCT2) substrate, due to altered kinetics of the drug(s) in these patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess these risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2778-4 A thorough QT trial designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

The timetable you submitted on August 21, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2015
Study Completion:	June 2016
Final Report Submission:	March 2017

2778-5 A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended-release tablets on the incidence of major adverse cardiovascular events (MACE) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. The primary objective of this trial should be to demonstrate that the upper bound of the 2-sided confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Contrave to that observed in the placebo group is less than 1.4. The trial should be designed to provide sufficient data to reflect the "on-treatment" cardiovascular risk associated with Contrave. Sample size calculation should take into account that "on-study" events would be censored 365 days after treatment discontinuation. The ongoing LIGHT trial will not be sufficient to meet this requirement; a new trial is required.

The timetable you submitted on September 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2015
Trial Completion:	July 2021
Final Report Submission:	January 2022

2778-6 Conduct a single-dose pharmacokinetic trial in subjects with mild, moderate, and severe hepatic impairment. Include overweight and obese subjects in the trial population.

The timetable you submitted on August 21, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2015
Trial Completion:	November 2017
Final Report Submission:	August 2018

2778-7 Conduct a single-dose pharmacokinetic trial in subjects with mild, moderate, and severe renal impairment. Include overweight and obese subjects in the trial population.

The timetable you submitted on August 21, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2015
Trial Completion:	November 2016
Final Report Submission:	August 2017

2778-8 Conduct a drug-drug interaction clinical trial with organic cation transporter 2 (OCT2) substrate, such as metformin, to evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to inhibit OCT2. The trial should test the single-dose pharmacokinetics of the organic cation transporter 2 (OCT2) substrate with and without co-administration of Contrave (preferably at steady-state after multiple doses).

The timetable you submitted on August 21, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2015
Trial Completion:	April 2016
Final Report Submission:	January 2017

Submit the protocols to your IND 068858, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required**

Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

JEAN-MARC P GUETTIER
09/10/2014