



NDA 200063/S-013

**SUPPLEMENT APPROVAL**

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

Dear Ms. Johnson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 14, 2017, and your amendments, 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.

This Prior Approval supplemental new drug application provides for revisions to the Adverse Reactions, Drug Interactions, and Clinical Pharmacology sections of the Contrave prescribing information (PI) to incorporate results from the studies conducted for the following postmarketing requirements (PMRs):

- 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.
- 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.
- 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).

We note that PMRs 2778-4 and 2778-8 were fulfilled per our letters issued June 14 and September 18, 2017, respectively.

## **APPROVAL & LABELING**

We have completed our review of this supplemental 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**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## **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 Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

### **FULFILLMENT OF POSTMARKETING REQUIREMENTS**

We have received your submission dated August 31, 2017, containing the final report for the following postmarketing requirement listed in the September 10, 2014, approval letter for NDA 200063:

- 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.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the September 10, 2014, approval letter that are still open.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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}*

Jennifer Rodriguez Pippins, MD, MPH  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling  
Prescribing Information  
Medication Guide (version approved May 2017)

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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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JENNIFER R PIPPINS  
06/13/2018