DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204242

NDA APPROVAL

Orexo AB
c/o DJA Global Pharmaceuticals, Inc.
115 Commons Court
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, RPh, MSc. Med. Chem.
President, DJA Global Pharmaceuticals, Inc.

Dear Ms. DeGraft-Johnson:

Please refer to your New Drug Application (NDA) dated September 5, 2012, received September 6, 2012, submitted on behalf of Orexo AB and pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zubsolv (buprenorphine and naloxone sublingual tablets), 1.4 mg/0.36 mg and 5.7 mg/1.4 mg.

We acknowledge receipt of your amendments dated October 5 and 28, and December 27, 2012, and February 26 and 28, April 8, 16, and 19, May 10 and 30, and June 7, 14, 20, and 21, 2013.

This new drug application provides for the use of Zubsolv for the maintenance treatment of opioid dependence.

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 and with the minor editorial revisions to the outer carton labeling listed below.

Remove the graphic above the proprietary name on the outer carton labeling.

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 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 & As* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels, except with the revisions listed above, 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* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf. 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 204242**." 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for neonates to 5 weeks of age because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. This drug product contains naloxone, which would provide no benefit for this pediatric group, but would expose them to risk.

Additionally, we are waiving the pediatric study requirement for ages 5 weeks through 16 years because necessary studies are impossible or highly impracticable. This is due to the low prevalence of opioid abuse and dependence in this population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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.

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 cardiac events related to your product. 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 this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess identify an unexpected serious risk of cardiac events, including life threatening arrhythmias, related to the use of Zubsolv.

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

2059-1 A clinical trial to assess the risk of QT prolongation with Zubsolv sublingual tablet, i.e., a thorough QT (tQT) trial.

The timetable you submitted via email on June 27, 2013, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	11/2013
Final Protocol Submission:	4/2014
Trial Completion:	4/2015
Final Report Submission:	1/2016

Submit the protocol to your IND 110637 with a cross-reference letter to this NDA. Submit all final report(s) 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) 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2059-2 Revise and validate the analytical method for organic impurities in the Naloxone API of the drug product accordingly to reflect an accuracy of (b) (4) RSD and intermediate precision of (b) (4) RSD.

The timetable you submitted on June 20, 2013, states that you will conduct this study according to the following schedule:

Final Report submitted as a Changes Being Effected (CBE-0) CMC Supplement:	8/2013

Submit clinical protocols to your IND 110637 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Zubsolv to ensure the benefits of the drug outweigh the (1) risks of exposure to Zubsolv sublingual tablet in persons for whom it was not prescribed, including accidental exposure in children, and (2) risks of abuse and misuse.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Zubsolv poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for

patients' safe and effective use of Zubsolv. FDA has determined that Zubsolv is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Zubsolv. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zubsolv.

Pursuant to 505-1(f)(1), we have also determined that Zubsolv can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of (1) exposure to Zubsolv sublingual tablet in persons for whom it was not prescribed, including accidental exposure in children, and (2) risks of abuse and misuse, that are listed in the labeling. The elements to assure safe use will inform prescribers, pharmacists, and patients of the serious risks associated with Zubsolv sublingual tablet and the appropriate conditions of safe use and storage of Zubsolv sublingual tablet. The elements to assure safe use will also ensure adequate clinical monitoring of patients by the healthcare providers.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on June 21, 2013, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Zubsolv into interstate commerce.

We also refer to your email communication dated June 7, 2013, stating your agreement to join the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) shared REMS program, and indicating that communication with the Buprenorphine Products Manufacturing Group (BPMG) has been initiated. Although your REMS is approved, when you join the BTOD shared REMS program, you will need to submit a modified REMS through the BPMG incorporating Zubsolv into the shared system.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of patients' understanding of the serious risks of Zubsolv;

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24;

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance;

d. An evaluation of prescribers' awareness and understanding of the serious risks associated with Zubsolv;

e. An evaluation of pharmacists' awareness and understanding of the serious risks associated with Zubsolv;

f. An analysis to evaluate utilization patterns of Zubsolv including frequency of office visits, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important to safe use;

g. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance will include, among other sources, reports of pediatric exposures;

h. Monitoring and evaluation of the implementation of the ETASU; and

i. An assessment of the extent to which the REMS is meeting its goals. Specific measures that will be proposed to increase awareness if surveys of patients, prescribers, and pharmacists indicate that awareness is not adequate.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204242 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204242 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 204242
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204242
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

EXPIRATION DATING PERIOD

Your packaging configurations of 30 sublingual tablets per carton (3 blister cards each with 10 tablets), for both strengths, is granted an 18 month expiration dating period, stored at 25ºC (77ºF) with excursions permitted to 15-30°C (59- 86°F).

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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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 Matt Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

BOB A RAPPAPORT
07/03/2013