



NDA 204242/S-015

SUPPLEMENT APPROVAL

Orexo US, Inc.
150 Headquarters Plaza
East Tower, 5th Fl
Morristown, NJ 07960

Attention: Michael Sumner, MD, MBA
Chief Medical Officer

Dear Dr. Sumner:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 6, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZUBSOLV (buprenorphine and naloxone) sublingual tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) risk evaluation and mitigation strategy (REMS) to align the REMS document and materials with the safety labeling changes approved in supplement S-014 on February 1, 2018. Those labeling changes pertained to the risks of life-threatening respiratory depression and death with concomitant use of buprenorphine with benzodiazepines or other CNS depressants, and included additional revisions to the Package Insert.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The waiver-granted shared system BTOD REMS, of which ZUBSOLV is a member, was originally approved on February 22, 2013. The most recent REMS modification was approved on May 23, 2017. 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 proposed modifications to the REMS consist of aligning the REMS document and materials to the labeling approved on February 1, 2018, as well as additional minor modifications, including updating the REMS document to the new format.

In accordance with section 505-1 of the FDCA, we have determined that the REMS modifications described above are necessary to ensure the benefits of the drug outweigh the risks.

Your proposed modified REMS, submitted to DMF 031588 on April 6, 2018, and appended to this letter, is approved.

The BTOD REMS currently includes the products listed on the FDA REMS website, available at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

Other products may be added to the BTOD REMS in the future if additional BTOD NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on September 4, 2013.

There are no changes to the REMS assessment plan described in our September 4, 2013, letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change.

Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application from using any element to assure safe use 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.

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

NDA 204242 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 204242/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 204242/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 204242/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204242/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 204242

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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 LCDR Mark A. Liberatore, PharmD, RAC, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director of Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JUDITH A RACOOSIN
10/31/2018