NDA 204242/S-026

SUPPLEMENT APPROVAL

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

Attention: Edward Kim, MD, MBA
Chief Medical Officer

Dear Dr. Kim:

Please refer to your supplemental new drug application (sNDA) dated and received March 17, 2023, and your amendments, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zubsolv (buprenorphine and naloxone) sublingual tablets.

This Changes Being Effected sNDA provides for proposed modifications to the approved Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) risk evaluation and mitigation strategy (REMS).

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) REQUIREMENTS

The Shared System (SS) REMS for BTOD products, of which Zubsolv is a member, was originally approved on February 22, 2013, and the most recent REMS modification was approved on December 16, 2022. The SS REMS consists of 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 updating the REMS Document to change the target audience for dissemination of communication materials and to align with the guidance for industry *Format and Content of a REMS Document* and the technical specifications document, *REMS Document Technical Conformance Guide*.[1] Additionally, references to withdrawn products, Drug Addiction Treatment Act of 2000, and office visits were removed. Finally, messaging regarding buprenorphine dosing, naloxone use, and counseling and psychosocial support was streamlined throughout

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the REMS. The following materials were revised: Appropriate Use Checklist, Dear Prescriber Letter, Dear Pharmacist Letter, Prescriber Brochure - Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers, Pharmacist Brochure - Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists, and REMS Website screenshots.

Your proposed modified REMS, submitted to Drug Master File (DMF) (b) (4) on March 15, 2023, amended and appended to this letter, is approved.

This shared system REMS, known as the BTOD REMS, currently includes products listed on the FDA REMS website[2].

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

The timetable for submission of assessments of the REMS remains the same as that approved on May 3, 2022.

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

Program Outreach and Communication (provide data for previous and current reporting periods (in yearly intervals within the reporting periods), and cumulatively)

1. Medication Guide Distribution and Dispensing
    a. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
    b. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
2. Distribution of Stakeholder Letters
    a. Number of BTOD REMS Program materials (i.e., Dear Prescriber Letter, Dear Pharmacist letter, Prescriber Brochure, Pharmacist Brochure, and Appropriate Use Checklist) sent via mail and email. Include the number of returned or undeliverable letters or undeliverable emails and the success rates.
3. REMS Website
    a. Number of visits and unique visits to the REMS Program website
    b. Number of Medication Guides accessed

Program Implementation and Operations (provide data for previous and current reporting periods (in yearly intervals within the reporting periods), and cumulatively)

[2] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

4. REMS Contact Center
    a. Number of contacts by stakeholder type
    b. Summary of reasons for calls by reporter
    c. Summary of frequently asked questions (FAQs) by stakeholder type
    d. Summary report of REMS-related problems identified and resulting corrective actions
5. BTOD REMS Specialists' Activity

    Reports on the BTOD REMS specialists' activity will include, but will not be limited to the following:

    a. Number of REMS specialists available
    b. Number of prescribers contacted per specialist
    c. Number of prescribers provided a copy of the REMS materials who requested or did not receive the REMS materials
    d. Number of prescribers who were provided additional follow-up information about the BTOD REMS via the following options:
        i. Option I: a live online meeting to review BTOD REMS requirements
        ii. Option II: a field visit to review BTOD REMS requirements
6. REMS Compliance
    a. Prescriber adherence to ETASU
7. Utilization Data
    a. An analysis to evaluate utilization patterns of buprenorphine-containing products including frequency of medical appointments, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important for safe use.

Knowledge (provide data per reporting period)

8. An evaluation of patients' awareness and understanding of the serious risks associated with buprenorphine-containing products.
9. An evaluation of prescribers' awareness and understanding of the serious risks associated with buprenorphine-containing products
10. An evaluation of pharmacists' awareness and understanding of the serious risks associated with buprenorphine-containing products
11. Specific measures to increase awareness if surveys of patients, prescribers, and pharmacists indicate that awareness is not adequate

Health Outcomes and/or Surrogates of Health Outcomes (provide data for previous and current reporting periods (in yearly intervals within the reporting periods), and cumulatively)

12. Safety Surveillance
    a. 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.
        i. Surveillance data on unintentional pediatric (ages 0 through 5 years) exposures and deaths involving buprenorphine-containing products and comparators. Content (i.e., tables, figures) and structure (i.e., organization of data sources and outcome measures) of these data should follow those of the data reported in the previous BTOD REMS Assessment reports.

Overall Assessment of REMS

13. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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 that 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 information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

> The Buprenorphine Product Manufacturers Group (BPMG) should submit the proposed knowledge survey protocols including the survey instruments for FDA review within 90 days of the date of this letter to DMF (b) (4) Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission as **"DMF (b) (4) REMS ASSESSMENT METHODOLOGY – SURVEY METHODOLOGIES"**.

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 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.

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

or

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.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, email Sandrine Ly, PharmD, Safety Regulatory Project Manager, at Sandrine.Ly@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

CDR Mark A. Liberatore, PharmD, RAC
Deputy Director for Safety
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Office of New Drugs
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/

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