DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020732/S-012
NDA 020733/S-016

SUPPLEMENT APPROVAL

Indivior Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Bruce Paolella
Director, Regulatory Affairs

Dear Mr. Paolella:

Please refer to your Supplemental New Drug Applications (sNDA) dated January 16, 2015, and received January 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subutex (buprenorphine) sublingual tablets (S-012) and Suboxone (buprenorphine and naloxone) sublingual tablets (S-016).

We acknowledge receipt of your amendments dated June 16, and July 28 and 30, 2015.

These "Prior Approval" supplemental new drug applications provide for modifications to the approved risk evaluation and mitigation strategies (REMS). These supplements are in response to our December 12, 2014, REMS Modification Notification letter.

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 REQUIREMENTS

The risk evaluation and mitigation strategies (REMS) for both Subutex sublingual tablets and Suboxone sublingual tablets were originally approved on December 22, 2011. Each REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to ensure the benefits of Subutex sublingual tablets and Suboxone sublingual tablets outweigh their risks, we determined that you were required to make the following REMS modifications:

- Addition of the following information:
  - Language on buccal administration of Suboxone (buprenorphine and naloxone) sublingual film.
  - A change to the indication for Suboxone (buprenorphine and naloxone) sublingual film to include the use of Suboxone (buprenorphine and naloxone) sublingual film in all phases of treatment for opioid dependence.

        - Limitations of use in initial treatment to patients physically dependent on heroin or other short-acting opioids.
    - A new warning regarding use in patients with hepatic impairment.
    - Updated language on use in pregnancy, nursing mothers, and patients with hepatic impairment.
- Incorporation of information related to two approved transmucosal buprenorphine-containing products, Bunavail (buprenorphine and naloxone film) and Zubsolv (buprenorphine and naloxone tablets), into the REMS materials.
- Updates to the appended REMS materials to reflect information on how approved buprenorphine and naloxone fixed-combination drugs differ from each other, how to switch between products, and recommended dosing.
- Removal of Appendix A: Obtaining Eligibility to Prescribe Suboxone or Subutex
- Revisions to the appended REMS materials to convey information in a clearer, more concise manner, provide greater emphasis on safety messages, and remove information found to be unnecessary.

In our December 12, 2014, letter, we also encouraged you to:

- Consolidate the three product-specific REMS into a single REMS encompassing Subutex sublingual tablets, Suboxone sublingual tablets, and Suboxone sublingual film.
- Develop a REMS website that includes information on the consolidated REMS for Subutex sublingual tablets, Suboxone sublingual tablets, and Suboxone sublingual film.

Your proposed modified REMS, submitted on July 30, 2015, and appended to this letter, are approved.

Your modified REMS must be fully operational no later than 30 calendar days from the date of this letter.

The timetables for submission of assessments of the REMS will remain the same as that approved on December 22, 2011. There are no changes to the REMS assessment plan described in our December 22, 2011, 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 of 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). 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 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 020732
NDA 020733 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 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 020732
NDA 020733 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020732/S-000; NDA 020733/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020732/S-000; NDA 020733/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020732/S-000; NDA 020733/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020732/S-000; NDA 020733/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 020732/S-000; NDA 020733/S-000

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Judith Racoosin, MD, MPH
Deputy Director for 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 and this page is the manifestation of the electronic signature.

/s/

JUDITH A RACOOSIN
09/22/2015