NDA 020732/S-017
NDA 020733/S-021
NDA 022410/S-030

SUPPLEMENT APPROVAL

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

Attention: Vanita Dimri, MS, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Dimri:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received July 21, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBUTEX (buprenorphine) sublingual tablets (NDA 020732/S-017), SUBOXONE (buprenorphine and naloxone) sublingual tablets (NDA 020733/S-021), and SUBOXONE (buprenorphine and naloxone) sublingual film (NDA 022410/S-030).

These Prior Approval supplemental new drug applications propose modifications to the approved risk evaluation and mitigation strategy (REMS) for SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film. The REMS was modified to align the REMS document and materials with the safety labeling changes for medication assisted treatment (MAT) products approved on December 16, 2016, that addresses the addition of language related to neonatal opioid withdrawal syndrome (NOWS) to the Warnings and Precautions Section of the Prescribing Information.

These supplements are in response to our July 6, 2017, REMS Modification Notification communication.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for SUBOXONE (buprenorphine and naloxone) sublingual film was originally approved on August 30, 2010. The REMS for SUBUTEX (buprenorphine) sublingual tablets and the REMS for SUBOXONE (buprenorphine and naloxone) sublingual tablets were originally approved on December 22, 2011. Each REMS was most recently modified on July 7, 2016, to consolidate the three product-specific REMS into a single REMS. 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.

In order to ensure the benefits of SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film outweigh the risks of accidental overdose, misuse, and abuse, we determined that you were required to make modifications consistent with the safety labeling changes approved on December 16, 2016, to the following REMS materials,:

- the *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers Brochure*
- the *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists Brochure*
- the Dear Prescriber Letter
- the Dear Pharmacist Letter
- the *Appropriate Use Checklist*
- the REMS website

Your proposed modified REMS, submitted on July 21, 2017, and appended to this letter, is approved.

The timetables for submission of assessments of the REMS remain the same as that approved on December 22, 2011.

There are no changes to the REMS assessment plan described in our July 13, 2017, 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 020732
NDA 020733
NDA 022410 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 these NDAs must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under one or more of these NDAs, 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
NDA 022410 REMS ASSESSMENT

NEW SUPPLEMENT FOR
NDA 020732/S-000, NDA 020733/S-000, and NDA 022410/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR
NDA 020732/S-000, NDA 020733/S-000, and NDA 022410/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR
NDA 020732/S-000, NDA 020733/S-000, and NDA 022410/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR
NDA 020732/S-000, NDA 020733/S-000, and NDA 022410/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, NDA 020733, and NDA 022410

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.

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 Mark Liberatore, PharmD, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. 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

DOCKET ALARM

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