NDA 209819/S-019

SUPPLEMENT APPROVAL

Indivior, Inc.
10710 Midlothian Turnpike, Suite 125
North Chesterfield, VA 23235

Attention: Rachel Capone, MSHS
Manager, Global Regulatory Affairs Strategy and CMC

Dear Ms. Capone:

Please refer to your supplemental new drug application (sNDA) dated and received April 2, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use.

This "Changes Being Effected" sNDA provides for proposed modifications to the approved SUBLOCADE 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 REMS for SUBLOCADE was originally approved on November 30, 2017, and the most recent REMS modification was approved on June 15, 2020. The REMS consists of 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 changes in response to recent updates with the Drug Enforcement Administration (DEA) interim final rule (IFR) published on November 2, 2020, that amended regulations for consistency with the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act of 2018 (the SUPPORT Act). REMS materials were updated to clarify that the pharmacy can deliver SUBLOCADE to either the prescribing practitioner or the practitioner administering the controlled substance, as applicable. Materials affected include the REMS Fact Sheet and the REMS Website.

Your proposed modified REMS, submitted on April 2, 2021, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on November 30, 2017.

We also refer to your submission dated August 5, 2020, which included proposed revisions to the REMS Assessment Plan. Additionally, your submission dated July 30, 2021, amended supplement S-019, and incorporated the following changes in the REMS Assessment Plan:

- Addition of metrics
    - Number of wholesalers/distributors deactivated resulting from audit findings
    - Summary of the subset of adverse events resulting in an outcome death
- Changing “analyses” to “analysis” throughout the assessment plan
- Removal of hyphens in “out-patient”, and spelling out of the acronym “DoD” (Department of Defense)

After reviewing your supplement amendment containing your proposed revised REMS Assessment Plan, we agree with the changes and your revised REMS Assessment Plan is as follows:

Program Implementation and Operations

1. REMS Operations and Utilization (per reporting period and cumulatively)
    a. Number of certified entities
        i. Healthcare settings that dispense SUBLOCADE
            - Number of healthcare settings that received at least one shipment of SUBLOCADE
        ii. Pharmacies that dispense SUBLOCADE
            - Number of pharmacies that received at least one shipment of SUBLOCADE
    b. Number of wholesalers/distributors shipping SUBLOCADE
        i. Number of wholesalers/distributors that received at least one shipment of SUBLOCADE from the manufacturer for distribution to healthcare settings and pharmacies
    c. Call Center Report
        i. Number of contacts
        ii. Summary of reason for call (Examples include “enrollment question, location of certified healthcare setting, etc.”) by

reporter (prescriber, authorized representative, healthcare setting, pharmacy, patient/caregiver, other)

iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues.

2. REMS Compliance (per reporting period and cumulatively)

a. Number of audits of certified healthcare settings, pharmacies and wholesalers/distributors or other audits conducted

i. Provide the number of expected audits and the number of actual audits conducted, reasons why expected audits weren't conducted, and plan to audit these entities

ii. Number of de-certified pharmacies and healthcare settings resulting from audit findings

iii. Number of wholesalers/distributors deactivated resulting from audit findings

iv. Summary of all corrective actions and any resulting preventative actions resulting from audit findings for each non-compliant entity

v. Provide a copy of the audit plan to include a description of audit classifications

vi. Provide unique identifiers for each stakeholder to track deviations over time

vii. Provide a copy of the non-compliance plan

b. Number of shipments of SUBLOCADE to non-certified healthcare settings or pharmacies, or other locations (e.g., patient's home), source of report, and corrective actions to prevent shipment to non-certified settings and pharmacies.

i. Disposition of SUBLOCADE shipped to non-certified healthcare settings and pharmacies (e.g., drug returned, drug administered)

c. Any other SUBLOCADE REMS non-compliance, source of report and resulting corrective actions

Health Outcomes and/or Surrogates of Health Outcomes

3. Safety surveillance

a. For each reporting period and cumulatively, provide analyses of all cases of:

i. Known or suspected intravenous administration of SUBLOCADE regardless of outcome, and a root cause analysis of the REMS processes that were not followed which may have led to intravenous administration

From sources including, but not limited to:

1. Adverse event reports
2. Literature search
3. Internet surveillance

With the analysis, provide a case line listing, overall summary, and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

ii. Serious adverse events related to thromboembolic disorders reported with SUBLOCADE. With the analysis, provide a case line listing, overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

iii. Known or suspected abuse, misuse, and overdose of SUBLOCADE, regardless of outcome

From sources including, but not limited to:

1. Adverse event reports
2. Literature search
3. Internet surveillance

With the analysis, provide a case line listing, overall summary, and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

b. Provide a summary of the subset of adverse events resulting in an outcome death

Program Outreach and Communication

4. REMS Outreach and communication (per reporting period and cumulatively)

a. Number, dates, and means of delivery for the letters sent (and packets, as appropriate)

b. Name of professional societies receiving REMS letters or other materials

c. Source of the list of prescribers, pharmacists, professional societies, pharmacies, wholesalers/distributors, hospitals, closed

health systems, outpatient clinics, long-term care facilities, Department of Defense facilities, prisons, inpatient psychiatric units, and Opioid Treatment Programs

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 supportthe 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 209819 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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.

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 209819 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 209819/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 209819/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 209819/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 2098919/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 209819

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

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 Jessica Voqui, PharmD, MS; Associate Director for Postmarket Regulatory Science, at (301) 796-2915.

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
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/

MARK A LIBERATORE
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