U.S. FOOD & DRUG ADMINISTRATION

NDA 205637/S-022

SUPPLEMENT APPROVAL

BioDelivery Sciences International, Inc.
4131 ParkLake Avenue, Suite 225
Raleigh, NC 27612

Attention: Sheila Whight
Regulatory Affairs Agent

Dear Ms. Whight:

Please refer to your supplemental new drug application (sNDA) dated and received February 8, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bunavail (buprenorphine and naloxone) buccal film.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) risk evaluation and mitigation strategy (REMS). This supplement is in response to our November 19, 2021, REMS Modification Notification letter.

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, of which Bunavail is a member, was originally approved on February 22, 2013, and the most recent REMS modification was approved on October 31, 2018. The SS 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 Bunavail outweigh its risks , we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated November 19, 2021. You additionally proposed to update REMS materials to include Subutex and Suboxone products.

Your proposed modified REMS, submitted to Drug Master File (DMF) 031588, on February 4, 2022, amended and appended to this letter, is approved.

This shared system REMS, known as the Buprenorphine Transmucosal Products for Opioid Dependence (BTOD), currently includes products listed on the FDA REMS website[1].

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

The surveillance data on unintentional pediatric exposures and death (12.a.i.) must be submitted annually, beginning with the REMS Assessment due August 30, 2022. All of the items below (1-13) must be submitted biennially, beginning with the REMS Assessment due August 30, 2023.

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, and Appropriate Use Checklist) sent via mail. Include the number of returned or undeliverable letters and the mailing 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)

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

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

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 (stratified by the number of new prescribers vs. existing prescribers contacted)
   c. Number of prescribers who requested information about the REMS
   d. Number of prescribers who were provided with REMS materials during the visit/meeting/call

6. REMS Compliance

   a. Prescriber adherence to ETASU

7. Utilization Data

   a. An analysis to evaluate utilization patterns of BTOD products including frequency of office visits, 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 BTOD products
9. An evaluation of prescribers' awareness and understanding of the serious risks associated with BTOD products
10. An evaluation of pharmacists' awareness and understanding of the serious risks associated with BTOD products
11. A proposal of specific measures to increase awareness if survey results of patients (metric 8), prescribers (metric 9), and pharmacists (metric 10) 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)

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.e., 12.a.i.).

i. Surveillance data on unintentional pediatric (ages 0 through 5 years) exposures and deaths involving BTODs and comparators. Content (i.e., tables, figures) and structure (i.e., organization of data sources and outcome measures) of these data must follow that of the data reported in the previous BTOD REMS Assessment reports.

Overall Assessment

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 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.

Within 90 days after receipt of this letter, update your supporting document to include the assessment plan above.

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 205637 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.

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 205637 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 205637/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205637/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 205637/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 205637/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 205637

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[2]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[3] Information and Instructions for completing the form can be found at FDA.gov.[4]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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[2] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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