NDA 210136/S-011

CORRECTED SUPPLEMENT APPROVAL

GENERAL ADVICE

Braeburn Inc.
450 Plymouth Road
Suite #400
Plymouth Meeting, PA 19462

Attention: Ruchira Kannambille
Senior Director, Regulatory Affairs

Dear Ruchira Kannambille:

Please refer to your supplemental new drug application (sNDA) dated and received June 30, 2025, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brixadi (buprenorphine) extended-release injection.

We also refer to our letter dated August 29, 2025. That letter contained the following error: missing REMS enclosure.

This corrected letter incorporates the correction of the error.

The effective date will remain August 29, 2025, the date of the original letter.

This Changes Being Effected sNDA provides for proposed modifications to the approved Brixadi 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 Brixadi was originally approved on May 23, 2023, and the most recent modification was approved on March 28, 2025. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of the following:

- Removal of the option to mail the Healthcare Setting and Pharmacy Enrollment Form to the Brixadi REMS Program.

- Changes to the Healthcare Setting and Pharmacy Enrollment Form to include asterisks indicating required fields and a statement regarding the need to submit a new enrollment form if the address of a REMS certified healthcare setting or pharmacy changes.
- Updates to the REMS website due to a change in the REMS administrator.

Your proposed modified REMS, submitted on June 30, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on May 23, 2023.

General Advice

We also refer to your submission dated June 17, 2025, and amendments, containing a revised REMS assessment plan, which incorporated the changes required per the April 18, 2025, REMS Assessment Acknowledgment/REMS Assessment Plan Revision letter.

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

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted:

REMS Program Implementation and Operations

1) Program Implementation (for the 6-month REMS assessment only)
    a. Date of first commercial distribution of Brixadi
    b. Date that the REMS website went live
    c. Date when healthcare settings or pharmacies could become certified by fax, mail, email, and online
    d. Date first healthcare setting or pharmacy became certified
    e. Date when the REMS Call Center is fully operational

2) REMS Certification
    a. Healthcare Settings
        i. Total number of certified healthcare settings
        ii. Number and percentage of newly certified healthcare settings stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility,

institution, opioid treatment program, Department of Defense (DoD) facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by United States (U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of healthcare setting type

iii. Number and percentage of certified healthcare settings that have received at least one Brixadi shipment during the reporting period stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility, institution, opioid treatment program, Department of Defense (DoD) facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by United States (U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of healthcare setting type

iv. Number and percentage of certified healthcare settings that have dispensed Brixadi at least once during the reporting period stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility, institution, opioid treatment program, Department of Defense (DoD) facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by United States (U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of healthcare setting type

b. Pharmacies

i. Total number of certified pharmacies

ii. Number and percentage of newly certified pharmacies stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by United States (U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of pharmacy type

iii. Number and percentage of certified pharmacies that have received at least one Brixadi shipment during the reporting period, stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by United States

(U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of pharmacy type

iv. Number and percentage of certified pharmacies that have dispensed Brixadi at least once during the reporting period, stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by United States (U.S.) Census)

a. For any healthcare setting under the category of “other”, provide the number and subcategories of pharmacy type

c. Wholesaler/Distributors

i. Total number of authorized wholesalers/distributors (including third-party logistics [3PL] companies), stratified by wholesalers/distributors and 3PL

ii. Number and percentage of newly authorized wholesalers/distributors (including 3PL companies), stratified by wholesalers/distributors and 3PL

iii. Number and percentage of active wholesalers/distributors (i.e., have shipped Brixadi at least once during the reporting period) (including 3PL companies), stratified by wholesalers/distributors and 3PL

3) REMS Utilization

a. Number of Brixadi shipments from wholesalers/distributors stratified by shipment location (i.e., healthcare setting, pharmacy, or other location):

i. Certified healthcare setting

ii. Certified pharmacy

iii. Non-certified healthcare setting

iv. Non-certified pharmacy

v. Other unintended location/recipient

b. Number of Brixadi shipments from 3PL companies, stratified by shipment location:

i. Certified healthcare setting

ii. Certified pharmacy

iii. Non-certified healthcare setting

iv. Non-certified pharmacy

v. Other unintended location/recipient

c. Number of Brixadi dispenses (first-fills and subsequent fills) stratified by dispensing entity (i.e., healthcare setting or pharmacy). Provide the data source used.

d. Number of unique patients prescribed Brixadi, stratified by dispensing entity (i.e., healthcare setting or pharmacy)

e. Number of Brixadi injections administered at a pharmacy stratified by pharmacy type (i.e., specialty, retail, other)

    i. For any healthcare setting under the category of "other", provide the number and subcategory of pharmacy type

4) REMS Infrastructure and Performance

a. Brixadi REMS Call Center Report

    i. Number of contacts by participant type

    ii. Summary of reason for calls (e.g., "enrollment question, location of certified healthcare setting, etc.") by reporter (i.e., prescriber, authorized representative, healthcare setting, pharmacy, patient/caregiver, other) accompanied by a description of the top five reasons for calls by each participant or 80% of calls by each participant (whichever accounts for the greater number of calls)

    iii. The number of REMS issues/complaints reported to the REMS Call Center, accompanied by a description of the top five reasons for calls by each participant or 80% of calls by each participant (whichever accounts for the greater number of calls) and the resolution (if applicable)

    iv. A summary and analysis of calls that may indicate an issue with patient access, or burden on the healthcare delivery system. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues.

    v. A summary report of corrective actions resulting from issues identified

    vi. The number of REMS materials requested through the REMS Call Center

b. REMS Website

    i. Number of visits and unique visits to the Brixadi REMS website

    ii. The number of REMS materials downloaded or printed for each material

5) REMS Compliance

a. Provide a report of audit findings for each participant (i.e., certified healthcare settings, pharmacies, wholesalers/distributors, third-party logistic companies, REMS Call Center, or other entities) including but not limited to:

i. A copy of the audit plan for each participant (including any auditing surveys or protocols used)

ii. The number of audits expected, number of audits conducted, and number of eligible participants for audit in each group. Include reasons why expected audits were not conducted and plans to audit these entities.

a. Initial healthcare setting audits

b. Initial pharmacy audits

c. Annual healthcare setting audits

d. Annual pharmacy audits

iii. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for group of audited participants

iv. Summary report of deviations found, associated corrective and preventive action (CAPA) plans resulting from audit findings for each non-compliant entity, and the status of CAPA plans

v. Provide follow-up information regarding whether each CAPA plan for a REMS participant was completed within the specified timeframe. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken.

vi. Use a unique ID for participants that had deviations to track deviations by participants over time

vii. Confirm documentation of completion of training for relevant staff

viii. Verify the existence of documented processes and procedures for complying with the REMS

ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. Provide a summary of the non-compliance identified, including but not limited to:

i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each participant, actions taken to address non-compliance for each event, and under what circumstances a participant would be suspended or de-certified from the REMS

ii. The number of instances of non-compliance, accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:

1. The unique identifier (ID(s)) of the participant(s) associated with the non-compliance event or deviation to enable tracking over time
2. The source of the non-compliance data
3. The results of the root cause analysis
4. What action(s) were taken in response and whether any follow-up is planned

iii. Number of healthcare settings and pharmacies decertified, reasons for decertification, and actions to address non-compliance

iv. Number of wholesalers/distributers deauthorized, reasons for deauthorization, and actions to address non-compliance

v. Number of shipments of Brixadi 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, or other locations. Provide the data source for this metric and each metric below.

1. Disposition of Brixadi shipped to non-certified healthcare settings or pharmacies, or other locations
    a. Number of returned shipments of Brixadi to wholesaler/distributor and/or 3PL provider
    b. Number of lost or stolen shipments of Brixadi reported to wholesaler/distributor and/or 3PL provider
    c. Number of Brixadi administrations at non-certified healthcare setting, pharmacy, or other location.
2. If the established threshold for metric 5.b.v. is not met, a root cause analysis of why the threshold was not met,

and a proposed plan for specific measures or modifications to the REMS to meet the established threshold

vi. Number of Brixadi dispenses directly to patients stratified by dispensing entity (i.e., healthcare setting or pharmacy). Provide the data source for this metric and each metric below.

1. Disposition of Brixadi dispenses directly to patients
2. If the established threshold for metric 5.b.vi. is not met, a root cause analysis of why the threshold was not met, and a proposed plan for specific measures or modifications to the REMS to meet the established threshold

vii. Verification that the pharmacy's designated authorized representative remains the same annually. If different, include the number of new authorized representative and verification of healthcare setting and pharmacy recertification

Health Outcomes and/or Surrogates of Health Outcomes

6) Safety surveillance

For each analysis, provide an overall summary, including a root cause analysis, and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication. The safety surveillance sources should include, but not be limited to: adverse event reports, literature searches, and internet surveillance.

a. Provide analyses of all cases of:

i. Known or suspected IV administration of Brixadi, regardless of outcome, and root cause analyses of what REMS processes were not followed and allowed for IV administration

ii. Serious adverse events related to thromboembolic disorders reported with Brixadi

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

b. Provide an analysis of adverse events resulting in an outcome of death

Program Outreach and Communication

7) REMS outreach and communication

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

        i. The number and percentage of emails successfully delivered, opened, and unopened

        ii. The number and percentage of mailings successfully delivered and those returned as undeliverable

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

    c. Source of the list of prescribers, pharmacists, professional societies, pharmacies, distributors, hospitals, closed health systems, outpatient clinics, long-term care facilities, DoD facilities, prisons, inpatient psychiatric units, and Opioid Treatment Programs.

Overall Assessment of REMS Effectiveness

8) 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.

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 210136 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 210136 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 210136 S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 210136/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 210136/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 210136/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 210136/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, 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/

MARK A LIBERATORE
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