CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesiology, Addiction Medicine, and Pain Medicine

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NDA#:	210136
Product:	BRIXADI (buprenorphine) depot injection
Applicant:	Braeburn Pharmaceuticals
From:	CDR Mark A. Liberatore, PharmD, RAC
Date:	*See DARRTS signature block*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

BRIXADI (buprenorphine) is an extended-release subcutaneous depot injection intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI is intended to be administered only by a healthcare provider. The pre- and postmarketing experience of other buprenorphine-containing products used for the treatment of OUD (e.g., Suboxone Film (NDA 022410), Zubsolv Tablet (NDA 204242), Cassipa film (NDA

208042), and other buprenorphine transmucosal products for opioid dependence) indicates that there are specific risks that must be considered due to the misuse and abuse of these products.

BRIXADI is designed to be injected subcutaneously in the buttock, thigh, abdomen, or upper arm. Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades.

Because buprenorphine-containing products are sought for illicit use, and because this is an injectable form of the product, the potential exists for a person to misuse the drug by injecting this product intravenously, if the product is dispensed directly to the person in an outpatient setting. Furthermore, because the BRIXADI product forms a gel when injected, and could be potentially catastrophic if injected intravenously, this combination of sought-after drug paired with the potential danger of the dosage form poses a unique risk, one that must be mitigated beyond professional labeling.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for BRIXADI to ensure that the benefits of the drug outweigh the risk of serious harm or death resulting from intravenous self-administration.

In reaching this determination, we considered the following:

A. BRIXADI is a buprenorphine depot subcutaneous injection intended for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. In the 2021 National Survey on Drug Use and Health, an estimated 2.5 million people aged 12 or older had an opioid use disorder.[1]

B. Opioid use disorder is a serious and life-threatening condition associated with morbidity and mortality due to overdose, blood-borne and sexually-transmitted diseases, and a variety of psychosocial consequences.

C. BRIXADI is effective in the treatment of opioid use disorder as measured by frequency of illicit drug use and retention in treatment.

[1] Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2022, Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health, HHS Publication No. PEP22-07-01-005, NSDUH Series H-57, https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report.

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D. Treatment with BRIXADI may continue indefinitely and should continue for as long as patients are benefiting, and the use of BRIXADI contributes to the intended treatment goals.

E. Because of the liquid crystalline delivery System, BRIXADI possesses a risk of embolism or thrombosis that may result in serious harm or death should the product be misused and injected intravenously. Known or potential adverse events associated with buprenorphine, the drug substance in BRIXADI, include abuse and accidental overdose leading to potentially lethal respiratory depression. Abuse and accidental overdose are common in the population of patients addicted to opioids, as are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances. Other adverse events related to buprenorphine include elevated liver enzymes, sedation, somnolence, and nausea. Other adverse events related to the injection include injection site reactions.

F. BRIXADI is not a new molecular entity.

The elements of the REMS will be elements to assure safe use, including that pharmacies, practitioners, or health care settings that dispense the drug are specially certified, an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	May 23, 2023
Nexus TTT #	2022-3005
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Somya Dunn, MD Katherine Hyatt Hawkins Shaw, PhD Page Crew, PharmD, MPH, BCPS (DMAMES)
Team Leader(s)	Shelly Harris, ScD, MPH (DMAMES) Carolyn Tieu, PharmD, MPH
Associate Director	Jo Wyeth, PharmD (OMEPRM)
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 18, 2023
Subject	Review of Proposed REMS
Established Name	Buprenorphine extended-release injection
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Partial Opioid Agonist
Formulation(s)	Supplied as a pre-filled syringe in two formulations (for subcutaneous administration): Weekly formulation: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly formulation: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) is an addendum to the December 20, 2018, December 01, 2020, and December 07, 2021 Risk Evaluation and Mitigation Strategy (REMS) reviews and evaluates the proposed REMS for Brixadi (buprenorphine extended-release injection) New Drug Application (NDA) 210136, submitted by Braeburn Inc. (Applicant) on November 23, 2022 and amended on January 13, 2023, March 22, 2023, April 05, 2023, and April 14, 2023.

The proposed indication for Brixadi is for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. The application was granted a tentative approval with a REMS on December 21, 2018, but received multiple Complete Responses (on January 19, 2018, December 01, 2020, and December 15, 2021) for facilities deficiencies.

It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU includes healthcare setting and pharmacy certifications (ETASU B). As part of the certification, the healthcare settings and pharmacies are required to establish processes and procedures to ensure that Brixadi is not dispensed directly to a patient; train all relevant staff that Brixadi must be dispensed directly to a healthcare provider for administration by a healthcare provider; and must not be dispensed to the patient.

DRM and DMAMES find the proposed REMS for Brixadi (buprenorphine extended-release injection) as submitted on April 14, 2023 to be acceptable for approval.

1. Introduction

This is an addendum to the December 20, 2018,[1] December 01, 2020,[2] and December 07, 2021[3] Risk Evaluation and Mitigation Strategy (REMS) reviews and evaluates the proposed REMS for Brixadi (buprenorphine extended-release injection) New Drug Application (NDA) 210136, submitted by Braeburn Inc. (Applicant) on November 23, 2022 and was amended on January 13, 2023, March 22, 2023, April 05, 2023, and April 14, 2023.

2. Background

2.1. Product Information

Brixadi is a partial opioid agonist proposed for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.[4]

Brixadi is supplied in two formulations: the weekly formulation (50 mg/mL concentration) is available in 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, and 32 mg/0.64 mL strengths. The monthly formulation (356 mg/mL concentration) is available in 64 mg/0.18 mL, 96 mg/0.27 mL, and 128 mg/0.36 mL

strengths. Weekly doses cannot be combined to yield an equivalent monthly dose.[4] Brixadi is injected into the subcutaneous tissues of the buttock, thigh, abdomen, or upper arm.

NDA 210136 was granted a tentative approval (TA) with a REMS on December 21, 2018.[5] It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS is comprised of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report. The ETASU includes healthcare setting and pharmacy certifications (ETASU B). For a full history of the product information and the rationale for the REMS, refer to our December 20, 2018 review.[1]

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 12/21/2018: The NDA 210136 and the REMS received TA
- 11/23/2022: Applicant resubmitted NDA 210136; the submission did not include the REMS
- 01/13/2023: Applicant submitted a REMS amendment to address changes to the Drug Addiction Treatment Act 2000 (DATA 2000) waiver requirement[6]
- 03/15/2023: Interim comments issued to the Applicant based on DRM's review of proposed REMS[7]
- 03/22/2023: Applicant submitted a REMS amendment
- 03/30/2023: Interim comments issued to the Applicant based on DRM's review of proposed REMS[8]
- 04/05/2023: Applicant submitted a REMS amendment
- 04/14/2023: Applicant submitted a REMS amendment

3. Review of Proposed REMS

3.1. REMS Goal

The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:

- Ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider.

Reviewer's Comments: *REMS goal is acceptable.*

3.2. REMS Requirements

3.2.1. Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements:

- ETASU B, Pharmacies and healthcare settings that dispense Brixadi are specially certified under 505-1(f)(3)(B)

Reviewer's Comments: *The Applicant's proposal for pharmacy and healthcare setting certification is acceptable.*

3.2.2. REMS Participant Requirements and Materials

3.2.2.1. Healthcare settings and pharmacies that dispense

Pharmacies and healthcare settings must become certified by designating an authorized representative to complete the certification process, oversee implementation, and compliance with the REMS. The authorized representative must certify in the REMS by completing and submitting the **Healthcare Setting and Pharmacy Enrollment Form** to the REMS. In addition, the authorized representative must train all relevant staff involved in dispensing that Brixadi must be dispensed directly to a healthcare provider for administration by a healthcare provider, and that Brixadi must not be dispensed to the patient. The following materials are associated with healthcare settings and pharmacies certification: **Healthcare Setting and Pharmacy Enrollment Form**.

Reviewer's Comments*: Refer to our March 15, 2023 and March 30, 2023 reviews for DRM's rationale for and changes that were needed for the form to be acceptable.*[7, 8] *The Applicant has addressed our comments. The proposed requirements and* ***Healthcare Setting and Pharmacy Enrollment Form*** *are acceptable.*

3.2.2.2. Wholesaler-distributors that distribute

Wholesalers-distributors will need to establish processes and procedures to ensure that Brixadi is distributed only to certified healthcare settings and pharmacies and train all relevant staff involved in distributing Brixadi.

Reviewer's Comments: *The proposed wholesaler-distributors requirements are acceptable.*

3.2.3. REMS Applicant Requirements and Materials

3.2.3.1. Communication

The Applicant proposed several communication activities to inform different stakeholders about the REMS and the risks and safe use of Brixadi.

The Applicant proposed targeting all healthcare providers who have prescribed buprenorphine for the treatment of OUD in the previous rolling 12-months in the U.S.; all pharmacies authorized by the Drug Enforcement Administration (DEA) to handle Schedule III controlled substances; and all opioid treatment programs certified under 42 CFR 8. Communication materials will be sent via mail or email within 60 calendar days of the approval of the REMS and again 6 months later. The Applicant will also disseminate communication materials to professional societies and professional meetings within the first year of approval of the REMS. Annually from the date of the approval of the REMS, the same communication materials will be sent to all new stakeholders of the above-referenced target audience.

The following materials are associated with communication materials and dissemination plan: **Healthcare Provider REMS Letter** and **Fact Sheet: How to Obtain Brixadi**.

Reviewer's comments*: Refer to our March 15, 2023 and March 30, 2023 reviews for DRM's rationale for and changes that were needed.[7, 8] The Applicant has addressed our comments. The proposed target audience, dissemination plan, and communication materials are acceptable.*

3.2.3.2. Operations

The Applicant proposed to establish and maintain a REMS Call Center and REMS Website to support stakeholders who interface with the REMS, as well as a establish and maintain a database of all REMS participants. The REMS website must include the capability to complete and submit the healthcare setting and pharmacy certification online, as well as the option to print the Prescribing Information, Medication Guide, and REMS materials. The Applicant will notify healthcare settings and pharmacies, confirming successful certification within 7 calendar days.

Reviewer's Comments: *The proposed REMS operations are acceptable.*

3.2.3.3. Compliance

To ensure REMS participants' compliance with the REMS requirements, the Applicant will verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the healthcare setting or pharmacy. The Applicant will also ensure processes and procedures are in place to maintain adequate records to demonstrate that REMS requirements are being met, including, but not limited to: Brixadi distribution and dispensing; certification of pharmacies and healthcare settings; and audits of REMS participants.

The Applicant must:

- Audit a representative sample of healthcare settings no later than 90 calendar days after the healthcare setting is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.
- Audit all pharmacies no later than 90 calendar days after the pharmacy is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.
- Audit all wholesalers-distributors no later than 90 calendar days after they become authorized, and audit all wholesalers-distributors annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

Reviewer's Comments*: The proposed compliance requirements as outlined in the REMS Document are acceptable.*

3.3. REMS Assessment Timetable

The Applicant must submit REMS assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.

Reviewer's Comments*: The first REMS assessment will occur at 6 months after approval of the REMS to ensure that DMAMES can review any emerging safety information related to the risk of serious harm or*

death that could result from intravenous self-administration. Brixadi will be labeled such that patients can start Brixadi after a single dose of a transmucosal buprenorphine product. This is a more rapid initiation period compared to a similar product, Sublocade (buprenorphine extended-release injection), which has a 7-day minimum buprenorphine containing product use period prior to first Sublocade injection. The REMS assessment timetable is acceptable.

4. Supporting Document

The REMS Supporting Document included the background and the Applicant's rationale for the REMS currently under review. The REMS Supporting Document contained the proposed methodologies for the REMS audit plan and noncompliance plan.

In addition, the REMS Supporting Document contains two Key Performance Indicators (KPIs) that will be used to determine if the REMS is meeting its goal of preventing intravenous self-administration of Brixadi by ensuring it is only dispensed to healthcare providers and not dispensed directly to the patient. The first proposed KPI is (b) (4) (b) (4) (b) (4) and the second proposed KPI is (b) (4)

Reviewer's Comments: *The Applicant has incorporated our comments from the March 15, 2023 and March 30, 2023 reviews in the REMS Supporting Document.*

As stated in the March 15, 2023 comments to the Applicant, if the NDA is approved, the Applicant should resubmit their audit plan and non-compliance plan methodologies within 60 days for Agency review. These methodologies were not formally reviewed during the current review cycle.

(b) (4)

(b) (4)

There are two key functions within the REMS objective: 1.) ensuring healthcare settings and pharmacies are certified and 2.) only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider.

(b) (4)

Both KPIs will need to be met to support that the REMS is meeting its goal.

4.1. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document. Refer to the Appendix for the final Assessment Plan.

Reviewer's Comments:

REMS Assessment Plan metrics were designed to evaluate whether the REMS is meeting its goal of mitigating serious harm or death that could result from intravenous self-administration, to evaluate if the REMS is functioning as designed, to determine if stakeholders are compliant with REMS requirements, and to assess issues with patient access and burden on the healthcare system.

The REMS Assessment Plan categories include Program Implementation and Operations, Utilization, Infrastructure and Performance; REMS Compliance; Health Outcomes and/or Surrogate of Health Outcomes; and Program Outreach and Communication.

The Applicant accepted the additional edits as described in the March 15, 2023[7] interim review to the REMS Assessment Plan. The REMS Assessment Plan is acceptable.

5. Discussion

Brixadi received a tentative approval (TA) with a REMS on December 21, 2018.[5] The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-

administration by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider.

The primary element employed in this REMS is healthcare setting and pharmacy certifications (ETASU B). As part of the certification, the healthcare settings and pharmacies are required to establish processes and procedures to ensure that Brixadi is not dispensed directly to a patient; and train all relevant staff that Brixadi must be dispensed directly to a healthcare provider for administration by a healthcare provider and must not be dispensed to the patient.

Until the end of 2022, buprenorphine prescribing for the treatment of OUD was limited to prescribers certified under Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of the new Consolidated Appropriations Act of 2023, healthcare providers will no longer be required to obtain the DATA 2000 waiver to prescribe buprenorphine for the treatment of OUD, nor will there be any limits or patient caps on the number of patients a prescriber may treat for OUD with buprenorphine. The DEA fully supports this significant policy reform, as it will increase the prescriber population and increase access to buprenorphine for those in need.[9] As a result, the REMS was updated to revise the target audience for dissemination materials (b) (4)

Additionally, the REMS materials were updated to align with the materials in the Sublocade REMS, which was most recently approved January 06, 2023. Sublocade is also an extended-release subcutaneous injection of buprenorphine and has the same risk as Brixadi for serious harm or death that could result from intravenous self-administration. As the targeted stakeholders for dissemination materials are likely to be the same group, closely aligning the materials in both REMS will help minimize confusion and will increase ease of use of the materials.

To determine the success of the Brixadi REMS, two KPIs were proposed that if met, would indicate that the REMS is meeting its goal of preventing intravenous self-administration. KPIs are measures that help determine if the REMS is functioning as designed, and whether the Brixadi REMS is achieving its goal of mitigating the risk of serious harm or death that could result from intravenous self-administration. The KPIs have been established for each part of the REMS objective, with thresholds informed by REMS experience with Sublocade. In addition, the KPIs may help determine if modifications to the REMS are necessary.

The two Brixadi REMS KPIs are as follows: (b) (4)

Lastly, to assess the impact of the REMS on patients and other stakeholders, the REMS Assessment Plan will collect more granular data to capture and quantify REMS implementation and utilization, and to identify burdens and access issues associated with the REMS.

6. Conclusions and Recommendations

DRM and DMAMES find the proposed REMS for Brixadi (buprenorphine extended-release injection) as submitted on April 14, 2023 acceptable.

7. References

[1] Dunn, S. Evaluation of Needs for a REMS review for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED December 20, 2018 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804cdeb2).

[2] Dunn, S. Evaluation of Proposed REMS review for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED December 01, 2020 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805b52f4).

[3] Dunn, S. Evaluation of Proposed REMS review for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED December 07, 2021 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8062fe4f).

[4] Braeburn. Proposed Prescribing Information for Brixadi (buprenorphine extended-release) November 23, 2022.

[5] Tentative Approval Letter for Brixadi (buprenorphine extended-release) injection. NDA 210136. December 21, 2018 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804ce586).

[6] SAMSHA-Removal of DATA Waiver (X-Waiver) Requirement. Updated January 25, 2023. Accessed March 3, 2023. https://www.samhsa.gov/medications-substance-use-disorders/removal-data-waiver-requirement

[7] Olumba, S. Review of Proposed REMS for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED March 15, 2023 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806ba28e).

[8] Olumba, S. Review of Proposed REMS for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED March 30, 2023 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806be1db).

[9] Drug Enforcement Administration. Diversion Control Division. Informational Documents. Accessed March 20, 2023. https://www.deadiversion.usdoj.gov/pubs/docs/index.html.

8. Appendix

REMS Assessment Plan

REMS Document

Enrollment Form

- Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

- Healthcare Provider REMS Letter
- Fact Sheet: How to Obtain BRIXADI

Other Materials

- REMS Website

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Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	May 23, 2023
Nexus TTT #	2022-3005
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Somya Dunn, MD Katherine Hyatt Hawkins Shaw, PhD Page Crew, PharmD, MPH, BCPS (DMAMES)
Team Leader(s)	Shelly Harris ScD, MPH (DMAMES) Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 30, 2023
Subject	Review of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Partial Opioid Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, and 128 mg subcutaneous injection

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1. Introduction

This review evaluates the Risk Evaluation and Mitigation Strategy (REMS) for Brixadi (buprenorphine extended-release) injection, New Drug Application (NDA) 210136, submitted by Braeburn Inc. (Applicant) on November 23, 2022.

Brixadi is a partial opioid agonist with the proposed indication for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 03/15/2023: Interim comments issued to the Applicant based on DRM's review of proposed REMS[1]
- 03/22/2023: Applicant submitted an amendment, subject of this review

3. Review of Proposed REMS

The Applicant did not incorporate all comments that were communicated to them on March 15, 2023. The Applicant also proposed the following change to the **Healthcare Setting and Pharmacy Enrollment Form,** by adding the underlined text:

(b) (4)

We do not agree with this change (b) (4) The Applicant will need to incorporate the comments sent on March 15, 2023 and remove the new text described above. In addition, the Applicant will need to add the key performance indicator (KPI) numerators and denominators the REMS Supporting Document.

Additionally, (b) (4) was proposed (b) (4) The Applicant will be requested to remove information (b) (4) from the REMS Document and add (b) (4) to the REMS Supporting Document.

4. Comments to the Applicant

The following comments and attached redlined REMS materials are based on our preliminary review of the proposed REMS submitted on March 22, 2023. Review of the proposed REMS is ongoing; these comments should not be considered final.

- The REMS Document has been edited to remove (b) (4) (b) (4) that is proposed (b) (4)

(b) (4)

Clarify how you intend to identify (b) (4) in the REMS Supporting Document.

- We do not agree with your addition of the text on the Healthcare Setting and Pharmacy Enrollment Form (see underlined text) that stated, (b) (4)

- The Healthcare Provider REMS Letter and REMS Program Fact Sheet have been updated to align with the REMS Document.

- Align the landing page of the REMS website to the sections and language in the Fact Sheet. See specific comments in the attached REMS website screen shots PDF.

- Apply changes made to REMS materials to the REMS website.

- Edits need to be made to the Supporting Document to align with the REMS Document, as well as to incorporate comments sent on March 15, 2023. Specifically, the timetable of assessment of reports and dissemination of communication materials need to be updated to occur within a period from the date of approval of REMS, rather than from a period after commercial availability. A statement regarding (b) (4) needs to be removed. In addition, the key performance indicator (KPI) numerators and denominators need to be updated to align with the revised KPIs.

Resubmission Instructions

Further changes are necessary for the REMS to be acceptable. Submit the following revised REMS materials within 2 business days that addresses these comments. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- REMS Document
- Healthcare Setting and Pharmacy Enrollment Form
- Dear Healthcare Provider Letter
- Fact Sheet: How to Obtain Brixadi
- REMS Website
- REMS Supporting Document

5. References

[1] Olumba, S. Review of Proposed REMS for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED March 15, 2023
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ba28e

[2] NAMSS Gateway: DEA Now Accepting Applications to Access Controlled Substances Act Registration Information Database. Updated January 22, 2021. Accessed March 27, 2023.
https://www.namssgateway.org/Article-Admin/dea-now-accepting-applications-to-access-controlled-substances-act-registration-information-database

6. Appendix

REMS Document

Enrollment Form

- Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

- Healthcare Provider REMS Letter
- Fact Sheet: How to Obtain BRIXADI

Other Materials

- REMS Website

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	May 23, 2023
OSE TTT#	2022-3005
Reviewer Name(s)	Stephanie Olumba, PharmD, MPH, BCPS Somya Dunn, MD Katherine Hyatt Hawkins Shaw, PhD Page Crew, PharmD, MPH, BCPS (DMAMES)
Team Leader	Shelly Harris, ScD, MPH (DMAMES) Carolyn Tieu, PharmD, MPH
Review Completion Date	March 15, 2023
Subject	Review of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Partial Opioid Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, and 128 mg subcutaneous injection

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1. Introduction

This review evaluates the Risk Evaluation and Mitigation Strategy (REMS) for Brixadi (buprenorphine extended-release) injection, New Drug Application (NDA) 210136, submitted by Braeburn Pharmaceuticals, Inc (Applicant) on November 23, 2022.

Brixadi is a partial opioid agonist with the proposed indication for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.[1]

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 12/21/18: The NDA 210136 and the REMS received tentative approval.
- 11/23/22: Applicant resubmitted NDA 210136; the submission did not include the REMS.
- 01/13/23: Applicant submitted a REMS amendment to address changes to the Drug Addiction Treatment Act 2000 (DATA 2000) waiver requirement.[2]

3. Review of Proposed REMS

The Applicant did not propose any changes to the REMS goals or REMS elements.

3.1. REMS Requirements

3.1.1. REMS Participant Requirements and Materials

Only the affected participants and their associated materials are reviewed below.

3.1.1.1. Health care settings and pharmacies that dispense

The Applicant did not propose any changes to the healthcare setting and pharmacies requirements or the **Healthcare Setting and Pharmacy Enrollment Form.**

Reviewer Comments: *Sublocade is also an extended-release buprenorphine injection approved for moderate to severe OUD. It was approved with a REMS to mitigate the risk of serious harm or death that could result from intravenous self-administration. The REMS goal, elements, and materials are nearly the same for the Sublocade and Brixadi REMS. Prescribers and other healthcare providers involved in the care of patients with OUD are likely to treat patients with Sublocade or Brixadi. On January 06, 2023, a minor REMS modification for the Sublocade REMS was approved to organize the REMS materials for clarity and to help minimize unnecessary stakeholder certifications. Applying what we have learned from Sublocade will help minimize confusion for these stakeholders; therefore, the Brixadi REMS materials (**Healthcare Setting and Pharmacy Enrollment Form**, **Healthcare Provider REMS Letter**, and **REMS Program Fact Sheet**) should be closely aligned for stakeholder ease of use. Edits have been provided to the **Healthcare Setting and Pharmacy Enrollment Form** and will be sent to the Applicant. See redlined version, attached.*

3.1.2. REMS Applicant Requirements and Materials

Only the affected Applicant requirements and their associated materials are reviewed below.

3.1.2.1. Communication

The Consolidated Appropriations Act of 2023 amended the Controlled Substances Act, so that prescribers do not need to be DATA 2000 waived to prescribe treatment for OUD and pharmacists do not need to verify that the prescription was written by a prescriber that is DATA 2000 waived.[2] The Applicant changed (b) (4) (b) (4) in the REMS Document (b) (4) During the first year following approval of the REMS, the Applicant changed the target audience from (b) (4) to "healthcare providers who (b) (4) buprenorphine for the treatment of opioid use disorder." The Applicant proposed (b) (4) For subsequent years, the Applicant changed the target audience from (b) (4) (b) (4) to "all new healthcare providers who (b) (4) buprenorphine for the treatment for opioid use disorder." The Applicant proposed using the Symphony Health Solutions database to identify healthcare providers who use other medications for opioid use disorder.

Reviewer Comments*: The proposed changes to the REMS Document* (b) (4) (b) (4) *are acceptable. The proposed target audiences should be modified to healthcare providers that "prescribe" instead of* (b) (4) *to clarify that prescribers are the target audience. Additionally, the dissemination plan will need to be updated to reflect a time after the date of the approval of the REMS instead* (b) (4) *The Applicant will need to clarify if the dissemination plan is to mail or email the communication materials and revise as necessary. As written, the Applicant is doing both mail and email. Additionally, the REMS Document has been aligned with the Format and Content of a REMS Document Guidance for Industry 2023 and the REMS Document Technical Conformance Guide 2023.[3,4] See redlined version, attached.*

Brixadi REMS Dear Healthcare Provider Letter

The Applicant did not propose any changes to **Healthcare Provider Letter**.

Reviewer Comments: *As discussed above, The* ***Healthcare Provider Letter*** *has edits to align with Sublocade Healthcare Provider Letter. See redlined version, attached.*

Fact Sheet: How to Obtain Brixadi

The **Fact Sheet: How to Obtain Brixadi** was updated (b) (4)

Reviewer Comments: *The proposed changes to* ***the Fact Sheet: How to Obtain Brixadi*** *are acceptable. However, the fact sheet needs additional changes to align with Sublocade. See redlined version, attached.*

3.1.2.2. Operations

REMS Website

To address the changes due to the Consolidated Appropriations Act of 2023 on DATA 2000 waivers, the REMS website was updated [redacted] (b) (4) It was also updated to remove a typographical error (the letter "j") in the contact number for Brixadi REMS in the Duplicate Enrollment Notification section.

Reviewer Comments: *The proposed changes to the REMS Website are acceptable. However, additional changes are needed to align with Sublocade. See redlined version, attached.*

3.1.2.3. Compliance

The Applicant did not propose any changes to the audit requirements.

Reviewer Comments: *The audit requirements for healthcare settings and pharmacies will be updated to reflect the Agency's current thinking regarding a representative sample for audits. The current audit requirement states* [redacted] (b) (4) *The audit requirements in the REMS Document have been edited to change* (b) (4) *to a representative sample for pharmacies and healthcare settings. The audit requirements were revised to:*

13. Audit a representative sample of healthcare settings no later than 90 calendar days after the healthcare setting is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

14. Audit all pharmacies no later than 90 calendar days after the pharmacy is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

15. Audit all wholesalers-distributors no later than 90 calendar days after they become authorized, and audit all wholesalers-distributors annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

3.2. REMS Assessment Timetable

The Applicant did not propose any changes to the REMS Assessment Timetable, with REMS Assessments submitted at 6 months, 12 months, and annually thereafter from the date of approval of the REMS.

Reviewer Comments: *The timetable for submission of REMS Assessments is acceptable.*

4. Supporting Document

The REMS Supporting Document was changed [redacted] (b) (4) (b) (4) The Applicant updated the Supporting Document to include information [redacted] (b) (4) References regarding [redacted] (b) (4) were removed throughout the

text and figures. The Applicant proposed [redacted] The Applicant also submitted audit and non-compliance plans.

Reviewer Comments*: The Applicant will be asked to align the Supporting Document with changes made to the REMS Document, REMS materials, and REMS Assessment Plan.*

The Applicant will be sent comments to add information [redacted] in the Supporting Document [redacted].

We do not agree with the Applicant's use of the statement [redacted] The Applicant will be sent a comment to remove information regarding the [redacted] throughout the Supporting Document and REMS Assessment Plan.

REMS Audit and Non-Compliance Plans

If the NDA is approved, the audit and non-compliance plans should be revised as needed to align with the REMS and resubmitted as a REMS Assessment Methodology no later than 90 days before the assessment will be conducted.

4.1. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document.

The proposed REMS Assessment Plan included [redacted] The REMS Assessment Plan was updated [redacted]

Reviewer Comments:
We reviewed the proposed Brixadi REMS Assessment Plan included in the REMS Supporting Document submitted on January 13, 2023 and have the following specific recommendations for revisions to the REMS Assessment Plan:

[redacted]

Key Performance Indicator

Refer to the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) review dated October 14, 2021, where comments were provided for the Applicant to add a single key performance indicator (KPI) (b) (4) *After further discussion between DMAMES and DRM, the KPI will be revised to include two KPIs.* (b) (4) *These KPIs are measurable metrics that will capture shipments to non-certified locations and dispenses directly to patients as primary indicators of the REMS performance.*

In addition, the Applicant will be sent a comment to (b) (4) *add a new section, titled "Key Performance Indicators" before the REMS Assessment Plan section in the REMS Supporting Document. The new section should include the revised KPIs, along with the supporting rationale, and plans to evaluate the REMS if the KPI thresholds are not met.*

5. Conclusions and Recommendations

DRM does not find the proposed REMS for Brixadi (buprenorphine extended-release) as submitted on January 13, 2023 to be acceptable, as described in this review. Additional changes are necessary. Send the comments in Section 6 to the Applicant and instruct the Applicant to submit a REMS amendment within 5 business days.

6. Comments to the Applicant

The following comments and attached redlined Brixadi REMS Document, REMS Materials, and REMS Assessment Plan are based on our preliminary review of the proposed REMS submitted on January 13, 2023. Review of the proposed REMS is ongoing; these comments should not be considered final.

General Comments

- The Healthcare Setting and Pharmacy Enrollment Form, Healthcare Provider REMS Letter, and REMS Program Fact Sheet have been revised to clarify certification requirements and reorganize information for better understanding of the content.

REMS Document

- The REMS Document have been revised to change the proposed target audiences to healthcare providers that "prescribe" instead of (b) (4) to clarify that prescribers are the target audience and to align with the *Format and Content of a REMS Document Guidance for Industry 2023* and the *REMS Document Technical Conformance Guide 2023*.
- Additionally, it is not necessary to state (b) (4) in the REMS Document (b) (4). The audit requirements have been revised to:

  13. Audit a representative sample of healthcare settings no later than 90 calendar days after the healthcare setting is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

  14. Audit all pharmacies no later than 90 calendar days after the pharmacy is certified and receives its first shipment of Brixadi, and audit a representative sample annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

  15. Audit all wholesalers-distributors no later than 90 calendar days after they become authorized, and audit all wholesalers-distributors annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

- Align all materials and the Supporting Document with edits made to the REMS Document.
- See redline REMS Document for additional comments.

REMS Website

- Align the REMS website with edits to the REMS Document, Healthcare Setting and Pharmacy Enrollment Form, Dear Healthcare Provider Letter, and the Fact Sheet. See annotated REMS website screenshots.

REMS Supporting Document

- Align the Supporting Document with the edits made to the REMS Document, REMS materials, and REMS Assessment Plan.

- Add information (b) (4) in the Supporting Document (b) (4)
- We do not agree with your proposal to include the statement (b) (4) Remove this statement (b) (4) from the Supporting Document and REMS Assessment Plan.
- The (b) (4) were included in the REMS Supporting Document. After an action is taken on the NDA, the (b) (4) should be revised as needed to align with the REMS and resubmitted as a REMS Assessment Methodology no later than 90 days before the assessment will be conducted.

REMS Assessment Plan

- You proposed a key performance indicator (KPI) (b) (4)

  (b) (4)
- Remove (b) (4) and add a new section, titled "Key Performance Indicators" before the REMS Assessment Plan section in the REMS Supporting Document. The new section should include the revised KPIs, along with the supporting rationale, and plans to evaluate the REMS if the KPI thresholds are not met.
- There were numerous changes to the REMS Assessment Plan. The changes are summarized below and a clean version of the REMS assessment plan is provided for your reference.

(b) (4)

(b) (4)

Resubmission Instructions

Further changes are necessary for the REMS to be acceptable. Submit the following revised REMS materials within 5 business days that addresses these comments. Accept the track changes with which you agree in the Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. Ensure that all Word versions include a setting which the author of comments and revisions can be identified (not anonymous). The next submission to the Gateway should include Clean Word, Tracked Word, and pdf formatted versions of the following documents:

- REMS Document
- Healthcare Setting and Pharmacy Enrollment Form
- Dear Healthcare Provider Letter
- Fact Sheet: How to Obtain Brixadi
- REMS Website
- REMS Supporting Document, including the REMS Assessment Plan

7. References

[1] Braeburn. Proposed Prescribing Information for Brixadi (buprenorphine extended-release) November 23, 2022

[2] SAMSHA-Removal of DATA Waiver (X-Waiver) Requirement. Updated January 25, 2023. Accessed March 3, 2023. https://www.samhsa.gov/medications-substance-use-disorders/removal-data-waiver-requirement

[3] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *Format and Content of a REMS Document Guidance for Industry*; accessed March 3, 2023. https://www.fda.gov/media/77846/download

[4] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2023; *REMS Document Technical Conformance Guide*; accessed March 3, 2023. https://www.fda.gov/media/164344/download

[5] Bergquist, B. Evaluation of Proposed REMS review for Brixadi (buprenorphine extended-release) NDA 210136, DARRTED November 19, 2021 (available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8062a8a6)

8. Appendix

REMS Assessment Plan

REMS Document

Enrollment Form

- Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

- Healthcare Provider REMS Letter
- Fact Sheet: How to Obtain BRIXADI

Other Materials

- REMS Website

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 15, 2021
OSE RCM #	2017-1447
Reviewer Name(s)	Somya Dunn, M.D. Barbara Bergquist, Pharm.D.
Team Leader(s)	Carolyn Tieu, Pharm.D., M.P.H. Shelly Harris, ScD, M.P.H.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 7, 2021
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) (b) (4) subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

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Executive Summary

This is an addendum to the December 20, 2018 and December 1, 2020 risk evaluation and mitigation strategy (REMS) reviews and evaluates the proposed REMS for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated on June 15, 2021. Brixadi was granted a tentative approval with a REMS on December 21, 2018, for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. However, the application received a Complete Response on January 1, 2018 and again on December 1, 2020 for facilities deficiencies.

It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The REMS requirements include that pharmacies and healthcare settings that dispense and administer Brixadi must be certified and that Brixadi is not dispensed directly to a patient.

DRM finds the Brixadi REMS Document and REMS materials submitted on July 6, 2021 to be acceptable and the REMS Supporting Document and REMS Assessment Plan submitted on October 22, 2021, and amended December 1, 2021 to be acceptable. However, the finalized REMS materials will be contingent upon the approved labeling. Since the application will receive a complete response for facilities deficiencies, the Applicant will be requested to submit a complete REMS submission with the next resubmission.

1. Introduction

This is an addendum to the December 20, 2018 and December 1, 2020 risk evaluation and mitigation strategy (REMS) review and evaluates the proposed REMS for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (the Applicant) on July 6, 2021 and the REMS Supporting Document (SD) and REMS Assessment Plan submitted on October 22, 2021, and amended December 1, 2021. Brixadi was granted a tentative approval (TA) with a REMS on December 21, 2018, for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS is comprised of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report.

2. BACKGROUND

2.1 PRODUCT INFORMATION

Brixadi is a single entity drug-device combination product with a modified-release formulation of buprenorphine in a novel FluidCrystal™ technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in Brixadi, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was

approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA), codified at 21 U.S.C. 823(g).

On October 24, 2018, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) was passed and amended the Controlled Substance Act to allow a pharmacy to deliver a controlled substance to the practitioner, in accordance with a prescription, to be administered to a specific patient for maintenance or detoxification treatment.

Brixadi is proposed to provide sustained plasma levels of buprenorphine and is intended for the treatment of opioid use disorder (OUD). Brixadi is designed to be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Brixadi is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Brixadi, buprenorphine, is available currently as sublingual tablets and film, buccal film and as an implant indicated for medication-assisted treatment (MAT).

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this addendum:

- 12/20/2018: Dunn, S. NDA 210136 REMS Rationale Review
- 12/21/2018: The NDA received a TA due to 3-year exclusivity for Sublocade, a monthly depot of buprenorphine, which blocked the approval of Brixadi through November 30, 2020. This TA included a REMS.
- 01/01/2018: FDA issued a complete response letter issused due to facilities deficiencies.
- 06/01/2020: Applicant resubmitted the NDA with changes to the proposed REMS.
- 12/01/2020: DRM's review stated the proposed REMS submitted on June 1, 2020 and as amended on October 27, November 19 and 27, 2020, was acceptable; however the REMS Assessment Plan was still under review.
- 12/01/2020: FDA issued a complete response letter issued due to facility deficiencies.
- 06/15/2021: Applicant resubmitted the NDA; the submission included a REMS Supporting Document but the full REMS (document and materials) was not included.
- 07/02/2021: FDA issued an information request (IR) for the Applicant to submit a full REMS.
- 07/06/2021: Applicant submitted an amendment with the full REMS.
- 10/14/2021: DRM provided interim comments to the Applicant. Comments on the Assessment Plan, Audit Plan, and Non-Compliance Protocol.
- 10/22/2021: Applicant submitted an amendment with an updated REMS SD with the requested changes.
- 11/19/2021: DRM provided interim comments to the Applicant on the REMS SD, Assessment Plan, Audit Plan, and Non-Compliance Protocol.
- 12/01/2021: Applicant submitted amendment with an updated REMS SD with the requested changes.

3. Risk Assessment and Safe Use Conditions

Currently, all buprenorphine products indicated for medication-assissted treatment (MAT) of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS. Suboxone, Zubsolv and the buccal film Bunavail all contain naloxone.

As an injectable depot device designed for subcutaneous administration, Brixadi differs significantly from the sublingual and buccal formulations of buprenorphine but is similar to Sublocade. Brixadi would be available as 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) (b) (4) for subcutaneous injection. The Agency is concerned about abuse risks specific to this type of formulation and route of administration; Brixadi will be available in prefilled syringes with needles attached. The final product configuration is ready to inject and easier to inject than other formulations of buprenorphine. In addition, if Brixadi is injected intravenously (IV) which is not intended, the doses range from 8 mg (b) (4) and the formulation does not contain naloxone. These factors may enable abuse, misuse and overdose with this product and given the proposed indication, many patients prescribed this medication will have a history of IV drug abuse predisposing them to this risk. In addition, the Agency is concerned that potential adverse events (AEs) may result from IV injection such as tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression. Other risks associated with Brixadi are consistent with the class of opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS).

The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from IV self-administration and should be administered by a healthcare provider (HCP). Brixadi should not be dispensed to patients; therefore, the Agency is requiring a REMS with certification of all pharmacies and healthcare settings that dispense Brixadi to ensure that Brixadi is not dispensed directly to patients and therefore will prevent IV administration by patients.

4. Review of Applicant's Proposed REMS

The Applicant's REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report. The REMS requirements include that pharmacies and healthcare settings that dispense and administer Brixadi must be certified (ETASU B and C) and that Brixadi is not dispensed directly to a patient. The REMS program materials and REMS Document were completed before the December 2020 action. For this submission, the Applicant did not propose changes to the goals, requirements, materials or a timetable for submission of assessment reports. The REMS Document and materials submitted on July 6, 2021 are acceptable. However, the final materials will be contingent on the final labeling.

5. Supporting Document

The proposed REMS SD describes the Applicant's distribution plan, operations, non-compliance protocol and audit plan, and REMS program assessment audit questionnaire. The non-compliance protocol and audit plan included (b) (4)

(b) (4)

The REMS SD includes a (b) (4)

The REMS SD includes details regarding their audit plan methodology, audit survey questions and how the REMS Program Audit Survey will be utilized and evaluated. The non-compliance protocol includes (b) (4)

Reviewer's comments: *The Applicant's audit plan and non-compliance protocol addressed the comments provided in our October 13, 2020 and November 13, 2020 comments from the previous review cycle. Additional revisions were made in this review cycle in response to our October 14 and November 19, 2021 comments.*[1,2] *The Applicant amended their submission on December 1, 2021 and we find the REMS SD to be acceptable.*

6 REMS Assessment Plan

The REMS Assessment Plan (See Attachment A) is summarized in the REMS Supporting Document. Revisions to the assessment plan were described in our reviews and included the addition of headings to align with the assessment metrics. A summary of revisions to the assessment plan are as follows:

(b) (4)

[1] Bergquist B. NDA 210135, Evaluation of the proposed REMS. October 14, 2021. Reference ID 4872422

[2] Bergquist B. NDA 210135, Evaluation of the proposed REMS. November 19, 2021. Reference ID 4891931

(b) (4)

Assessment of the REMS Goal and Objective

The objective of the Brixadi REMS will be evaluated by using methods that assess compliance with safe-use behaviors and reports of adverse events.

Strategies to Directly Affect Knowledge of the REMS Program Requirements: Data on the dissemination of the *Healthcare Provider REMS Letter* and the *Fact Sheet: How to Obtain Brixadi* will inform on whether information on the REMS program were distributed by the Applicant to stakeholders and professional societies as required.

Strategies to Directly Affect Safe-Use Behavior: The objective of, "Ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider" will be assessed using data related to stakeholder certification and Brixadi dispensing and distribution data. In addition, compliance metrics and results of stakeholder audits will be used to inform whether stakeholders followed the REMS requirements for Brixadi dispenses.

Strategies to Inform Health Outcomes and/or Surrogates of Health Outcomes: (b) (4)

Key Performance Indicator (KPI): The Applicant and the Agency agreed on the following KPI which will be used to determine if the REMS is successful in meeting its risk mitigation goal of preventing IV self-administration of Brixadi by ensuring it is only dispensed to HCPs for administration and not handed directly to a patient. If the KPI is not achieved, the assessment plan includes metrics requiring the Applicant to provide a narrative of any process improvement measures or any root cause analysis that have been or need to be implemented. The KPI is defined below:

"The KPI is defined as: (b) (4)

The KPI is to be calculated as:

(b) (4)

Mapping of REMS goal, objectives and performance metrics to the Brixadi REMS Assessment Plan: This table maps the REMS goal and objective to the REMS requirements, materials, assessment metrics, data sources and performance thresholds and is used to illustrate the relationship between the REMS and the REMS Assessment Plan. A compliance threshold of (b) (4)% was mapped for the following objectives: (b) (4)

(b) (4)

Impact of the REMS on the Healthcare Delivery System

Multiple REMS Assessment Plan metrics can be used to determine if there are any potential burden or patient access issues associated with the REMS program requirements. (b) (4)

***Reviewer's comments**: The Brixadi REMS assessment plan submitted by the Applicant on December 1, 2021 is acceptable.*

5 Discussion

The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider.

For buprenorphine use in MAT, the Substance Abuse and Mental Health Services Administration (SAMHSA) manages the DATA 2000 in which providers (physicians, nurse practitioners, and physician assistants) can apply and hold waivers to prescribe and/or dispense buprenorphine products for MAT without holding a separate Drug Enforcement Agency registration for that specific purpose. SAMHSA sets eligibility and certification requirements as well as an interagency notification review processes for providers who apply. Buprenorphine treatment may be prescribed by providers with a DATA 2000 waiver in office practice settings.

Many of the buprenorphine products used to treat OUD are self adminintered and stored at home and as a result are more susceptible to misuse, abuse and accidental overdose. Respiratory depression and NOWS are risks that are associated with all opioid medications. However, this product is administered as once weekly or once monthly subcutaneous injection by a healthcare provider and if approved would provide an additional option for the treatment of OUD.

The Brixadi REMS will require healthcare setting and pharmacy certification. As part of the certification these entities are required to put policies and procedures in place to ensure that Brixadi is not dispensed directly to patients and train all relevant staff involved in dispensing that the drug must be dispensed directly to a healthcare provider for administration by a healthcare provider, and the drug must not be dispensed to the patient. The REMS for Brixadi is

comparable to the Sublocade (buprenorphine) REMS, which was approved November 30, 2017. Sublocade is also an extended-release formulation for subcutaneous for injection and has similar risks.

To determine the success of the Brixadi REMS, a key performance indicator (KPI) was proposed that if met, would indicate that the REMS is meeting its risk mitigation goal of preventing IV self-administration. Due to the need to consider a system that compensates for the limits of human ability, we believe this program would be successful if it can significantly minimize Brixadi being dispensed to a patient, so that these would be rare events. Thereby, the KPI has been defined as the percentage of Brixadi dispenses that are dispensed to a healthcare provider for administration and not directly to patients. This KPI is a process outcome based on the REMS processes and procedures implemented to ensure that Brixadi is never dispensed directly to a patient. These processes include requiring HCS and pharmacy certification to ensure these stakeholders establish procedures to meet the REMS requirements and train all relevant staff. Although the KPI is not linked to a health outcome, we believe that if processes implemented to ensure Brixadi is not dispensed directly to a patient are met, this will support mitigating the risk of IV self-administration.

To assess the impact of the REMS on patient outcomes, the assessment plan includes metrics (b) (4) This measure is not being utilized to determine the overall success of the REMS as it is dependent upon voluntary submission of adverse event reports and could be under-reported.

6 Conclusions

DRM finds the REMS amendment submitted on July 6, 2021 and amended on October 22, 2021 and December 1, 2021 acceptable. Due to the risk of serious harm or death that could result from intravenous self-administration, Brixadi must only be dispensed directly to a healthcare provider and healthcare settings and pharmacies must be certified. The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised and is acceptable.

7 Appendix

ATTACHMENTS

REMS Document

Healthcare Setting and Pharmacy Enrollment Form

Healthcare Provider REMS Letter

Fact Sheet: How to Obtain BRIXADI

REMS Website

REMS Assessment Plan

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 15, 2021
OSE RCM #	2017-1447
Reviewer Name(s)	Barbara Bergquist, PharmD
Team Leader	Shelly Harris, ScD, MPH
Deputy Division Director	Doris Auth, Pharm D
Review Completion Date	November 19, 2021
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	Subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

Table of Contents

1. Introduction

This review provides comments and suggested revisions to the proposed risk evaluation and mitigation strategy (REMS) for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (Braeburn) on July 6, 2021 and amended REMS Supporting Document on October 22, 2021. The Applicant's October 22, 2021 revised audit plan, non-compliance protocol and REMS assessment plan are the subject of this review.

2. Regulatory History

The following is a summary of the regulatory history relevant to the July 6, 2021 submission and this review:

- December 21, 2018 - Brixadi was granted a tentative approval (TA) with a REMS on for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.
- December 1, 2020 - Complete response letter issued for deficiencies found on facility inspections and prescribing information to conform to content and format regulations.
- July 6, 2021 – REMS submission
- October 22, 2021 – Amended Supporting Document (SD) and Assessment Plan submitted

3. Supporting Document

The Supporting Document (SD) includes the Applicant's proposed audit plan, (b) (4) and non-compliance protocol. A revised SD was submitted October 22, 2021 in response to our October 14, 2021[1] review.

Reviewer's comments:

(b) (4)

[1] October 14, 2021, DRM (B. Bergquist) REMS Review

(b) (4)

4. Assessment Plan

The Applicant submitted a revised REMS assessment plan (b) (4)

(b) (4)

Reviewer's comments:

(b) (4)

5. Conclusions and Recommendations

The submitted Brixadi REMS SD, audit plan and non-compliance protocol need revisions to align with stakeholder audit requirements as per the Brixadi REMS document. The table mapping of the REMS program (goals, objectives, stakeholder requirements and materials) to the REMS Assessment Plan (data sources, metrics, methodologies, performance thresholds) used to illustrate the relationship between the REMS program and the REMS Assessment Plan needs revision to align with the Brixadi REMS Document and capture the intent of the REMS as described in Section 4 of this review.

The revised assessment plan (b) (4) requires a minor typographical edit to be acceptable.

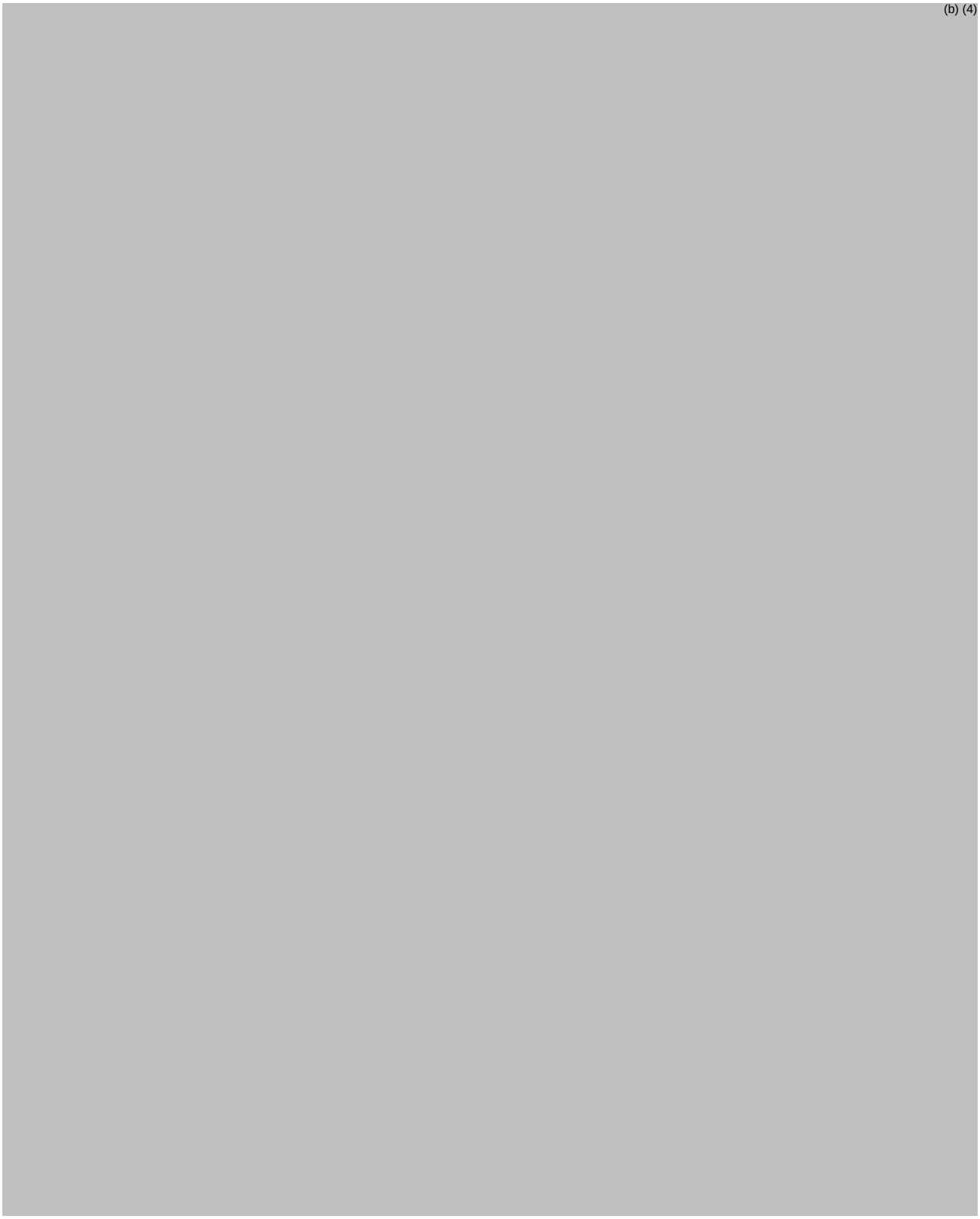
6. Comments for the Applicant

We have the following comments on the proposed REMS submitted on July 6, 2021 and the amended supporting document (SD) submitted October 22, 2021:

Your October 22, 2021 submission of the Brixadi REMS Supporting Document (SD) needs revision to ensure that REMS processes and procedures are in place, functioning and support the REMS requirements. We have the following comments:

REMS Supporting Document (SD)

(b) (4)



[redacted] (b) (4)

Update your Supporting Document to incorporate our comments above. **Resubmit the REMS Supporting Document by COB December 1, 2021.**

6. Appendix

Attachment: Revised Brixadi REMS Supporting Document – Word Version (Redline)

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 15, 2021
OSE RCM #	2017-1447
Reviewer Name(s)	Barbara Bergquist, PharmD
Team Leader	Shelly Harris, ScD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	October 14, 2021
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	Subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

Table of Contents

1. Introduction

This review provides comments and suggested revisions to the proposed risk evaluation and mitigation strategy (REMS) for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (Braeburn) on July 6, 2021. The Applicant's submitted audit plan, non-compliance protocol and REMS assessment plan are the subject of this review.

2. Regulatory History

The following is a summary of the regulatory history relevant to the July 6, 2021 submission and this review:

- December 21, 2018 - Brixadi was granted a tentative approval (TA) with a REMS on for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.
- December 1, 2020 - Complete response letter issued for deficiencies found on facility inspections and prescribing information to conform to content and format regulations.
- July 6, 2021 – REMS submission

3. Supporting Document

The Supporting Document (SD) includes the Applicant's proposed audit plan, (b) (4) and non-compliance protocol. The additions and revisions that we determined were necessary in our November 13, 2020[1] review were included in the SD submitted July 6, 2021.

(b) (4)

4. Assessment Plan

[1] November 13, 2020, DRM (B. Bergquist) REMS Review

The Applicant submitted a proposed REMS assessment plan (b) (4)

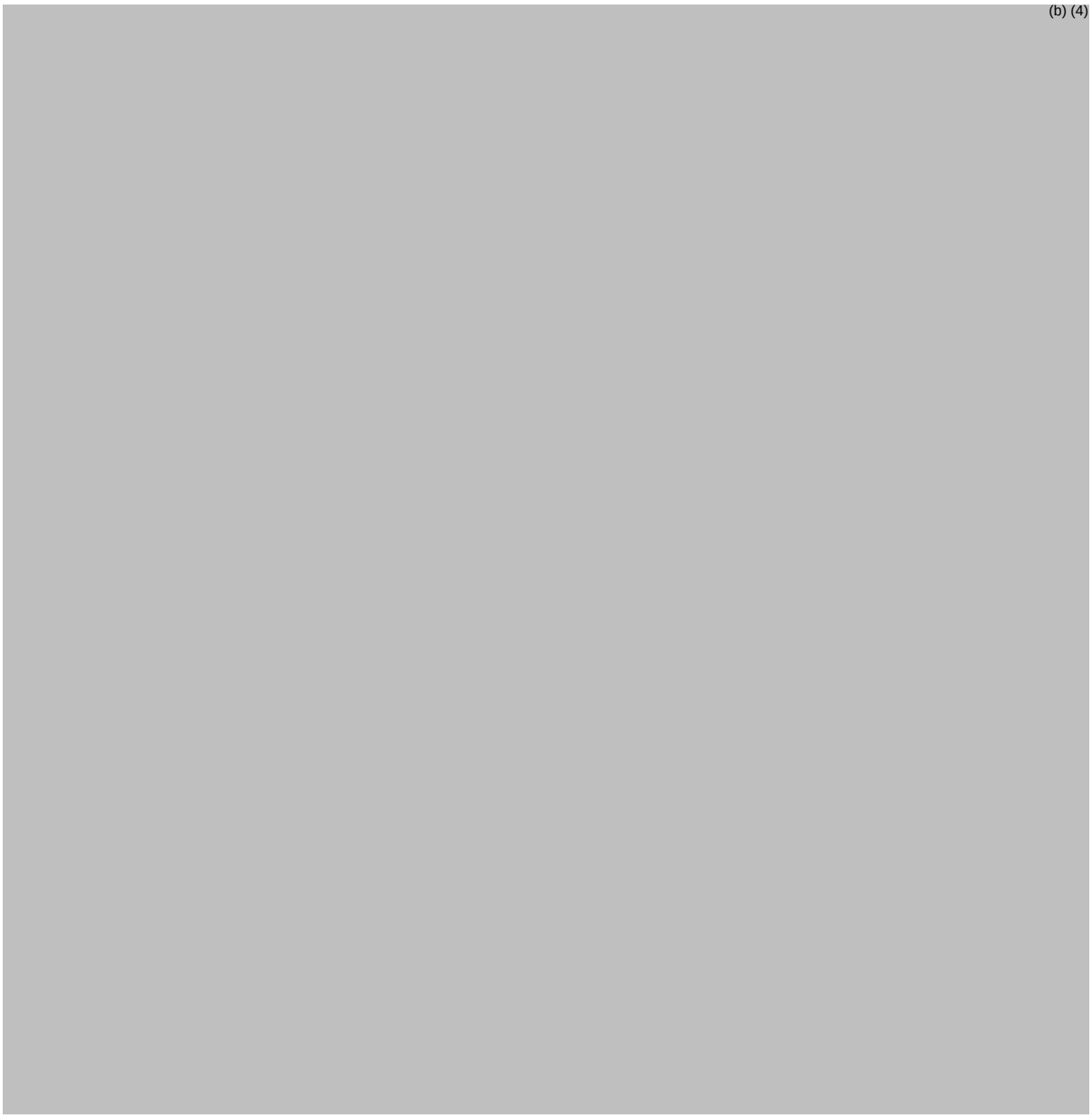
(b) (4)

Reviewer's comments: (b) (4)

(b) (4)

Appendix 2: Brixadi REMS Assessment Plan (pgs. 28-30)

(b) (4)



5. Conclusions and Recommendations

The submitted Brixadi REMS audit plan and non-compliance protocol need revisions to align with stakeholder audit requirements as per the Brixadi REMS document. The (b) (4) (b) (4) KPIs need revision as the performance thresholds proposed by the Applicant do not take into consideration the impact that human failings can have on the REMS operations and subsequent outcomes. In addition, the KPIs need to be expanded to include defining the numerator and denominator. The table mapping of the REMS program (goals, objectives, stakeholder requirements and materials) to the REMS Assessment Plan (data sources, metrics, methodologies, performance thresholds) used to illustrate the relationship between the REMS program and the REMS Assessment Plan needs revision to align with the Brixadi REMS Document as described in Section 4 of this review.

The assessment plan requires revisions to add a metric to capture data needed to inform on the KPI to include defining the numerator, denominator and the performance threshold.

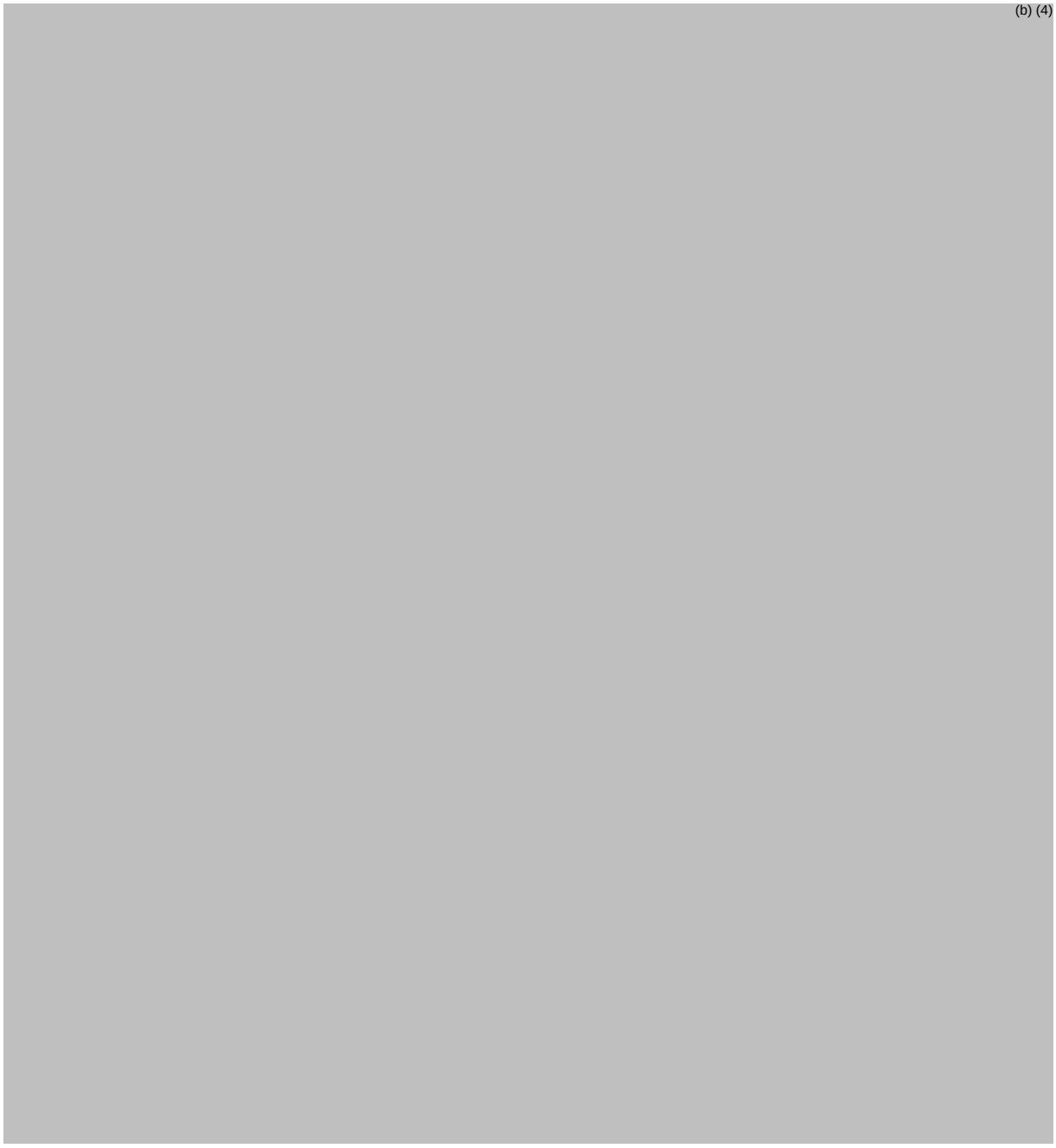
6. Comments for the Applicant

We have the following comments on the proposed REMS submitted on July 6, 2021.

Review of the audit plan, non-compliance protocol and assessment plan indicate that revisions and additional information are needed to ensure that REMS processes and procedures are in place, functioning and support the REMS requirements. We have the following comments:

REMS Supporting Document (SD)

(b) (4)



Update your Supporting Document to incorporate our comments above. Resubmit the REMS Supporting Document by COB October 22, 2021.

6. Appendix

Appendix A: Revised Brixadi REMS Assessment Plan

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 1, 2020
OSE RCM #	2017-1447
Reviewer Name(s)	Somya Dunn, M.D. Barbara Bergquist, Pharm.D. Joan Blair, R.N., M.P.H.
Team Leader(s)	Carolyn Tieu, Pharm.D., M.P.H. Shelly Harris, ScD, M.P.H.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 1, 2020
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) (b) (4) subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

1 INTRODUCTION

This is an addendum to the December 20, 2018 risk evaluation and mitigation strategy (REMS) review and evaluates the proposed REMS for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (Braeburn) on June 1, 2020 and amended on October 27, November 19, and November 27, 2020. Brixadi was granted a tentative approval (TA) with a REMS on December 21, 2018, for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments report.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Brixadi is a single entity drug-device combination product with a modified-release formulation of buprenorphine in a novel FluidCrystalTM technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in Brixadi, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA), codified at 21 U.S.C. 823(g). Brixadi is proposed to provide sustained plasma levels of buprenorphine and is intended for the treatment of opioid use disorder (OUD). Brixadi is designed to be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Brixadi is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Brixadi, buprenorphine, is available currently as sublingual tablets and film, buccal film and as an implant indicated for medication-assisted treatment.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- December 20, 2018: Dunn, S. NDA 210136 REMS Rationale Review
- December 21, 2018: The NDA received a TA due to 3-year exclusivity for Sublocade, a monthly depot of buprenorphine, which blocked the approval of Brixadi through November 30, 2020. This TA included a REMS.
- June 1, 2020: The NDA was resubmitted with the final TA REMS from December 21, 2018 with changes pertaining to (b) (4)
- October 13, 2020: Interim comments issued to the Applicant stating that the changes proposed were not acceptable.

- October 27, 2020: The Applicant sent a revised REMS submission removing the reference to (b) (4)
- November 13, 2020: Interim comments issued to the Applicant regarding the REMS Supporting Document.
- November 19, 2020: The Applicant submitted a revised REMS Supporting Document
- November 24, 2020: Interim comments issued to the Applicant regarding the REMS Supporting Document.
- November 27, 2020: The Applicant submitted a revised REMS Supporting Document.

3 CONCLUSION

DRM finds the REMS materials submitted on June 1, 2020 and amended on October 27, November 19, and November 27, 2020 acceptable; however, the Assessment Plan is still under review. Since the review division recommends a complete response due to facility concerns, DRM defers a final recommendation on the REMS at this time.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 1, 2020
OSE RCM #	2017-1447
Reviewer Name(s)	Barbara Bergquist, Pharm.D. Dunn, Somya, M.D.
Team Leader	Shelly Harris, ScD, MPH Carolyn Tieu, Pharm.D., MPH
Review Completion Date	November 13, 2020
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) (b) (4) subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

Table of Contents

1. Introduction

This review provides comments and suggested revisions to the proposed risk evaluation and mitigation strategy (REMS) for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (Braeburn) on June 1, 2020 and appended on October 27, 2020. Brixadi was granted a tentative approval (TA) with a REMS on December 21, 2018, for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report.

The Applicant submitted a revised REMS document, REMS supporting document, and REMS materials on October 27, 2020. The revised REMS supporting document is the subject of this review.

2. Regulatory History

The following is a summary of the regulatory history relevant to this October 27, 2020 submission:

- October 13, 2020: The Agency sent interim comments including that we determined that the audit plan and non-compliance protocol were not complete and needed revisions to include audit observation classifications, a description of non-compliance members and events and to populate a table mapping the REMS program to the REMS Assessment Plan. (Dunn, S. and Bergquist, B., Brixadi REMS Review, darrted October 13, 2020)
- October 27, 2020: REMS amendment received

3. Supporting Document

In their October 27, 2020 REMS amendment submission of the updated REMS supporting document (SD), the Applicant did not incorporate all of the Agency's comments provided on October 13, 2020 for the audit plan, non-compliance protocol, and the table of mapped REMS goals and objectives.

In addition, the updated REMS SD describes their plan (b) (4)

Reviewer's Comment: The revised audit plan, non-compliance protocol and the table of mapped REMS goals and objectives need further revision. In addition, the processes for medication dispensing in pharmacies needs further clarification.

<u>Audit Plan</u>: The revised audit plan included [redacted] (b) (4)

[redacted] (b) (4)

Non-Compliance Protocol: The revised non-compliance protocol included [redacted] (b) (4)

<u>Mapping of the REMS goal and objectives and performance metrics to the Assessment Plan:</u> The proposed [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

<u>Movement, Dispensing and Administration:</u> The Agency would like to understand in further detail how the Applicant plans to keep track of medications that are administered in a pharmacy when the medication is not dispensed there. They should describe if there are different codes for these processes for insurance billing purposes. If these will be different pharmacies, the Agency would

like to understand how the medication will move from one pharmacy where it is dispensed to another where it is administered. A description of how compliance with the processes and procedures implemented to ensure that the pharmacist administers the medication to the patient and the drug is not dispensed directly to the patient will be assessed should be provided.

4. Conclusions and Recommendations

The revised Brixadi REMS audit plan and non-compliance protocol need further revisions to be effective in monitoring compliance with the REMS program processes and procedures. The REMS Audit Plan methodology needs revision to include how the REMS Program Assessment Survey will be utilized and evaluated. The REMS Non-compliance Protocol needs revision to include a listing of operational guidelines and non-compliance events for healthcare settings.

The proposed mapping of the REMS program (goals, objectives, stakeholder requirements and materials) to the REMS Assessment Plan (data sources, metrics, methodologies, performance thresholds) used to illustrate the relationship between the REMS program and the REMS Assessment Plan needs revision and clarification. Additional mapping of program Implementation and Operations metrics are needed to further illustrate stakeholder certification. Clarification of proposed performance thresholds and additional performance thresholds are needed.

Further information regarding how the medication is dispensed and administered in the pharmacy setting, and how the Applicant plans to ensure compliance with this process is needed.

5. Comments for the Applicant

We have the following comments on the proposed REMS submitted on June 1, 2020 and appended on October 27, 2020. Review of the entire REMS proposal is ongoing: these comments should not be considered final.

REMS Supporting Document

The proposed mapping of the REMS program (goals, objectives, stakeholder requirements and materials) to the REMS Assessment Plan (data sources, metrics, methodologies, performance thresholds) used to illustrate the relationship between the REMS program and the REMS Assessment Plan (pgs. 28 and 29 of the REMS Supporting Document) needs revision and clarification as follows:

(b) (4)

(b) (4)

Audit Plan: The submitted audit plan needs revisions to include but are not limited to the following:

(b) (4)

Non-Compliance Protocol: The submitted non-compliance protocol needs revisions to include but are not limited to the following:

(b) (4)

Movement, Dispensing and Administration: The Agency would like to understand in further detail how you plan to keep track of medication that is administered in a pharmacy when the medication is not dispensed there. Describe if there are different codes for these processes for insurance billing purposes. If these will be different pharmacies, the Agency would like to understand how the medication will move from one pharmacy where it is dispensed to another where it is administered. Provide a description of how compliance with the processes and procedures implemented to ensure that the pharmacist administers the medication to the patient and the drug is not dispensed directly to the patient will be assessed; include a performance threshold for compliance and a rationale for the stated threshold.

Update your Supporting Document to incorporate our comments above. **Resubmit the REMS Supporting Document by COB November 19, 2020.**

6. Appendix

Appendix A: Sample mapping table for pharmacy certification

Appendix A: Sample Mapping table for pharmacy certification

Objective	Requirement	REMS Materials	Assessment Plan Category/Domain	Metrics	Data Sources/Analytical Tools	REMS Assessment Report:	Performance Threshold	Methodology/
					Analytical Tools	Frequency of Metric Reporting		Protocol Location and Date Submitted
Goal: X:								
2. Ensuring pharmacies that dispense and/or administer XX drug are certified	Pharmacy Certification	Designate an authorized representative: training, policies and procedures Pharmacy Enrollment Form	Implementation and operations	1. Pharmacy enrollment statistics	1. Applicant's REMS databases 2. Contracted databases	In 6 months, 12 month and annual reports	1. 99-100%	
	Safe Use Condition	1. Pharmacy must verify that HCS is certified before dispensing: a. REMS stakeholder training materials b. Stakeholder attestations on enrollment forms c. REMS website 2. Wholesaler/distributor must verify that pharmacy is certified before distribution of product a. contract with Applicant	Safe use behaviors	1. Non-compliance metrics: a. dispensed directly to a patient b. dispensed to non-certified HCS c. dispensed by non-certified pharmacy d. shipped to non-certified pharmacy 2. Audit results a. decertifications	1. Applicant's REMS databases 2. Any contracted databases by the Applicant 3. Audits 4. Non-compliance plan	In 6 months, 12 month and annual reports	1. 99-100%	
			Implementation and operations	1. Drug utilization statistics 2. Pharmacy enrollment 3. Pharmacy type	1. REMS Contact Center 2. REMS website 3. REMS Database 4. Contracted databases	In 6 months, 12 month and annual reports	1. 99-100%	
3. Ensuring healthcare settings are certified								

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 1, 2020
OSE RCM #	2017-1447
Reviewer Name(s)	Somya Dunn, M.D.
	Barbara Bergquist, Pharm.D.
Team Leader(s)	Carolyn Tieu, Pharm.D., MPH
	Shelly Harris, ScD, MPH
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	October 13, 2020
Subject	Evaluation of Proposed REMS
Established Name	Buprenorphine extended-release
Trade Name	Brixadi
Name of Applicant	Braeburn
Therapeutic Class	Opioid Partial Agonist
Formulation(s)	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) (b) (4) subcutaneous injection
Dosing Regimen	Once weekly or once monthly subcutaneous injection

Table of Contents

1. Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) for Brixadi (buprenorphine extended-release), New Drug Application (NDA) 210136 submitted by Braeburn Pharmaceuticals, Incorporated (Braeburn) on June 1, 2020. Brixadi was granted a tentative approval (TA) with a REMS on December 21, 2018 for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. It was determined that a REMS is necessary to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments report.

In the June 1, 2020 resubmission, Braeburn proposed changes to some of the REMS materials (b) (4) (b) (4) This proposal consists of edits to several of the Brixadi REMS materials, including the Fact Sheet, Healthcare Setting and Pharmacy Enrollment Form and the REMS Website.

2. Regulatory History

The following is a summary of the regulatory history relevant to this June 1, 2020 submission:

- December 20, 2018: Dunn, S. NDA 210136 REMS Rationale Review
- December 21, 2018: The NDA received a TA due to 3-year exclusivity for Sublocade, a monthly depot of buprenorphine, which blocked the approval of Brixadi through November 30, 2020. This TA included a REMS.
- June 1, 2020: The NDA was resubmitted with the final TA REMS from 12/21/18 with changes discussed in this review.

3. Review of Applicant's Proposed REMS

3.1 REMS Goal

The Applicant did not propose any changes to the goal. The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:

1. Ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider for administration by a healthcare provider.

Reviewer's Comment: The proposed goal is acceptable.

3.2 REMS Document

The REMS Document includes the following elements: elements to assure safe use (healthcare settings and pharmacies that dispenses the drug must be certified), implementation system, and a timetable for submission of REMS assessment reports. The Applicant did not propose any changes to the elements. However, the Applicant proposed using the term healthcare provider instead of healthcare professional.

Reviewer's Comment: The format and content of the REMS Document as well as the minor change to the REMS Document proposed by the Applicant is acceptable.

3.3 ELEMENTS TO ASSURE SAFE USE

Healthcare Settings and Pharmacy Certification

Brixadi is intended to be administered by a healthcare provider (HCP) and should not be handed directly to patients; therefore, the Agency is requiring a REMS with certification of all pharmacies and healthcare settings that dispense Brixadi. This certification will occur through the *Healthcare Setting and Pharmacy Certification Form*. This will help ensure that Brixadi is not handed directly to patients and therefore will mitigate the risk of patients self-administering Brixadi intravenously. The Applicant proposed a change (b) (4) (b) (4)

Reviewer's Comment: The Applicant's proposal (b) (4) (b) (4) *is not acceptable. This phrase is not a commonly used medical terminology and should not be included in REMS materials* (b) (4)

3.4 IMPLEMENTATION SYSTEM

Communication Materials and Dissemination Plans

The Applicant proposes a communication plan to inform HCP about the REMS and risks and safe use of Brixadi within 60 calendar days of when Brixadi is first distributed and again six months later. The targeted audience include all prescribers certified to treat opioid use disorder under the Drug Addiction Treatment Act of 2000 and all pharmacies authorized by DEA to handle schedule III controlled substances. The communication materials include the *Dear Healthcare Provider Letter* and the *REMS Program Fact Sheet*.

The Applicant has editorial changes to the Dear Healthcare Provider Letter and proposed language (b) (4) to the REMS Program Fact Sheet.

Reviewer's Comment: As stated above, (b) (4) *Therefore, the changes to the Fact Sheet are not acceptable. The editorial change proposed by the Applicant to the Dear Healthcare Provider Letter is acceptable.*

REMS Website

The Applicant proposed a change (b) (4) (b) (4) throughout the website.

Reviewer's Comment: As discussed, (b) (4)

Compliance

The Applicant proposes the following audit plans which were part of the TA:

(b) (4)

Reviewer's Comments: The Agency has the following changes to be in line with other recently approved REMS programs to ensure a representative sample of healthcare settings and pharmacies. These are as follows:

1. *Audit 10% of healthcare settings no later than 90 calendar days after they become certified, and 10% annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Annual audits must include healthcare settings that have received at least one shipment of Brixadi in the past 12 months and not have been audited in the past 3 years.*

2. *Audit pharmacies no later than 90 calendar days after the pharmacy receives its first shipment, and 10% annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Annual audits must include pharmacies that have received at least one shipment of Brixadi in the past 12 months and not have been audited in the past 3 years.*

3.5 TIMETABLE FOR SUBMISSION OF ASSESSMENT REPORTS

The Applicant did not propose any changes. The Applicant will be required to submit their reports at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS.

Reviewer's Comment: The proposed timetable is acceptable.

3 Supporting Document

The Supporting Document (SD) describes Braeburn's proposed distribution plan, proposed operations, proposed non-compliance protocol and audit plan, and proposed REMS program assessment audit questionnaire. The non-compliance protocol and audit plan included which stakeholders would be audited (distributors, pharmacies and healthcare settings), a brief description of the audit process and a table which included examples of non-compliance with the REMS by stakeholder. It also incorporates language from the proposed label and REMS Document. The Applicant has also included their plan to have patients directed by their prescriber to an injection center to receive their Brixadi injection.

Reviewer's Comment: The Supporting Document should be updated to align with edits to the REMS Document.

Healthcare centers that provide Brixadi injections for patients must meet the criteria set forth in the REMS Document. The Applicant is proposing (b) (4) *however, these descriptions can remain in the Supporting Document.*

(b) (4)

Agency would also like a description of the movement and administration of the medication, specifically in to retail pharmacies who may be administering the medication. The Applicant should describe if there were, or if there are going to be additional communication activities for these retail settings.

In addition, the Applicant must ensure that all types of settings are included in the audits for healthcare centers. They must describe how they will ensure that this will occur in the audit plan.

(b) (4)

<u>Audit Plan</u>: The number of audits of stakeholders needs revision as discussed in Section 3.4. The submitted audit plan needs revision to include classifications for audit observations and a more in-depth description of the audit methodology to include method of stakeholder audits (b) (4) *, the scope of the audits and criteria for when a risk-based approach for auditing would be implemented. Healthcare settings and pharmacies that acted as injection site centers where pharmacists have administered Brixadi to a patient should be included in stakeholder audits. The type of pharmacy audited should be reported (i.e. specialty, retail).*

<u>Non-Compliance Plan</u>: The non-compliance plan should include the definition, purpose and function of compliance staff, a complete listing of operational guidelines for each stakeholder to include a listing of non-compliance events that require assessment, intervention or escalation and a description of defined interventions including corrective and preventative actions (CAPA) plans and escalation procedures. A description of non-compliance events that result in deactivation and/or decertifications and procedures for reinstatement should be included. In addition, pre-determined thresholds for stakeholder compliance with the REMS requirements along with a rationale for these thresholds are needed.

A mapping of the REMS goal and objectives and performance metrics should be included in the supporting document to illustrate the relationship among the REMS program (goal, objectives, stakeholder requirements and materials) and the REMS Assessment Plan (data sources, metrics, methodologies and performance thresholds). An example table to be populated by the Applicant is provided.

4 REMS Assessment Plan

The Applicant submitted a proposed assessment plan. The assessment plan included metrics under the following categories: REMS operations and utilization, REMS Call Center report, REMS compliance, safety surveillance, REMS outreach and communication and program implementation.

Reviewer's comments: The metrics in the revised Brixadi REMS Assessment Plan are used to assess whether the REMS program is meeting its risk mitigation goal. Recommended revisions to the Brixadi REMS Assessment Plan include the following:

(b) (4)

(b) (4)

5 Conclusions and Recommendations

DRM does not find the proposed REMS submitted on June 1, 2020 acceptable.

Overall, DRM does not agree that the REMS materials need to include (b) (4) (b) (4) DRM does agree with the editorial changes made to the Dear Healthcare Provider Letter. The Agency would also like a description of the movement and administration of the medication in the Supporting Document.

The Brixadi REMS Assessment Plan needs revision to add metrics which will allow for further assessment of REMS program performance. Additional program implementation and operations metrics were added for more in-depth analysis of stakeholder participation in the REMS. Program outreach and communication metrics were added to assess the extent to which the REMS materials reach the intended stakeholders.

6 Comments for the Applicant

We have the following comments on the proposed REMS submitted on June 1, 2020.

Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within 2 weeks that addresses these comments. Include all appended materials and the REMS Supporting Document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, a .pdf version and a compiled REMS pdf document that excludes the Supporting Document.

The recommendations provided here are based on the current proposed labeling. However, all materials must be revised to be consistent with the final FDA-approved labeling.

REMS Goal

The proposed goal is acceptable.

REMS Document

The Agency has the following changes to the audit requirements to be in line with other recently approved REMS programs to ensure an adequate sample of healthcare settings and pharmacies. In the future the sample size for the audits may need to be revised to ensure that the audits provide a representative sample that can be generalized to the respective settings. The changes are as follows:

1. Audit 10% of healthcare settings no later than 90 calendar days after they become certified, and 10% annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Annual audits must include healthcare settings that have received at least one shipment of Brixadi in the past 12 months and not have been audited in the past 3 years.

2. Audit pharmacies no later than 90 calendar days after the pharmacy receives its first shipment, and 10% annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Annual audits must include pharmacies that have received at least one shipment of Brixadi in the past 12 months and not have been audited in the past 3 years.

See redlined REMS Document.

REMS Materials

- **Healthcare Setting and Pharmacy Enrollment Form**: Your proposal to include (b) (4) (b) (4) is not acceptable. This phrase is not commonly used medical terminology and should not be included in REMS materials (b) (4) Remove (b) (4) from all applicable REMS materials.
- **Dear Healthcare Provider Letter**: Your edits to Dear Healthcare Provider Letter are acceptable.
- **REMS Program Fact Sheet**: Remove references to (b) (4)
- **REMS Website**: Remove references to (b) (4)

REMS Supporting Document

The Supporting Document should be updated to align with edits to the REMS Document. The descriptions (b) (4) can remain in the Supporting Document.

(b) (4) Agency would like a description of the movement and administration of the medication, specifically in settings such as retail pharmacies, including who may be administering the medication in these settings. Describe if there were additional communication activities that took place for these retail settings or if there are additional communication activities that you are planning.

A mapping of the REMS goal and objectives and performance metrics should be included in the supporting document to illustrate the relationship among the REMS program (goal, objectives, stakeholder requirements and materials) and the REMS Assessment Plan (data sources, metrics, methodologies and performance thresholds).

Audit Plan: The audit plan is not complete. The submitted plan needs revisions to include but are not limited to the following:

(b) (4)

(b) (4)

- **Non-Compliance Plan:** The non-compliance is not complete. The submitted plan needs revisions to include but are not limited to the following:

(b) (4)

REMS Assessment Plan

See the redlined REMS Assessment Plan for revisions and comments.

7 Appendix

ATTACHMENTS

REMS Document

REMS Assessment Plan

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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/

SOMYA V DUNN
10/13/2020 12:17:43 PM

BARBARA A BERGQUIST
10/13/2020 12:25:43 PM

SHELLY L HARRIS
10/13/2020 12:27:39 PM

CAROLYN N TIEU
10/13/2020 12:34:35 PM

CYNTHIA L LACIVITA
10/13/2020 12:38:45 PM

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesia, Analgesia, and Addiction Products

NDA #:	**210136**
Product:	BRIXADI (buprenorphine) depot injection
Applicant:	Braeburn Pharmaceuticals
From:	Judith A. Racoosin, MD, MPH
Date:	*see DARRTS signature block*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

BRIXADI is a buprenorphine depot subcutaneous injection intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI is intended to be administered only by a healthcare provider. The pre- and postmarketing experience of other buprenorphine-containing products used for the treatment of OUD (e.g., SUBOXONE sublingual film, SUBOXONE tablets, SUBUTEX tablets, etc.) indicates that there are specific risks that must be considered due to the misuse and abuse of these products.

This product is a drug-device combination provided in prefilled syringes with multiple doses with two durations (weekly and monthly).

BRIXADI (weekly; 8, 16, 24, 32 mg) consists of 50 mg/mL buprenorphine base, 10% w/w anhydrous ethanol and soybean phosphatidylcholine/glycerol dioleate in a weight ratio 50/50 to final volume.

BRIXADI (monthly; 64, 96, 128 mg) consists of 356 mg/mL buprenorphine base, 30% w/w N-methyl pyrrolidine and soybean phosphatidylcholine/glycerol dioleate in weight ratio 40/60 to final volume.

BRIXADI is designed to be injected subcutaneously in the buttock, thigh, abdomen, or upper arm. Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades.

Because buprenorphine-containing products are sought for illicit use, and because this is an injectable form of the product, the potential exists for a person to misuse the drug by injecting this product intravenously, if the product is dispensed directly to the person in an outpatient setting. Furthermore, because the BRIXADI product forms a gel when injected, and could be potentially catastrophic if injected intravenously, this combination of sought-after drug paired with the potential danger of the dosage form poses a unique risk, one that must be mitigated beyond professional labeling.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for BRIXADI (buprenorphine) to ensure the benefits of BRIXADI (buprenorphine) outweigh the risk of serious harm or death resulting from intravenous self-administration.

In reaching this determination, we considered the following:

A. BRIXADI is a buprenorphine depot subcutaneous injection intended for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. In the 2017 National Survey on Drug Use and Health, an estimated 2.1 million people aged 12 or older had an opioid use disorder.[1]

B. Opioid use disorder is a serious and life-threatening condition associated with morbidity and mortality due to overdose, blood-borne and sexually-transmitted diseases, and a variety of psychosocial consequences.

C. BRIXADI is effective in the treatment of opioid use disorder as measured by frequency of illicit drug use and retention in treatment.

D. Treatment with BRIXADI may continue indefinitely and should continue for as long as patients are benefiting, and the use of BRIXADI contributes to the intended treatment goals.

E. Because of the liquid crystalline delivery System, BRIXADI possesses a risk of embolism or thrombosis that may result in serious harm or death should the product be misused and injected intravenously. Known or potential adverse events associated with buprenorphine, the drug substance in BRIXADI, include abuse and accidental overdose leading to potentially lethal respiratory depression. Abuse and accidental

[1] Substance Abuse and Mental Health Services Administration. (2018). Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

overdose are common in the population of patients addicted to opioids, as are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances. Other adverse events related to buprenorphine include elevated liver enzymes, sedation, somnolence, and nausea. Other adverse events related to the injection include injection site reactions.

F. BRIXADI is not a new molecular entity.

The elements of the REMS include:

a. Elements to assure safe use to ensure that health care settings and pharmacies that dispense BRIXADI are specially certified;
b. An implementation system; and,
c. A timetable for submission of assessments of the 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/

MATTHEW W SULLIVAN
12/21/2018

JUDITH A RACOOSIN
12/21/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210136
PDUFA Goal Date	December 26, 2018
OSE RCM #	2017-1447
Reviewer Name(s)	Somya Dunn, MD
Team Leader	Selena Ready, Pharm.D, DRISK
Division Director	Cynthia LaCivita, Pharm.D, DRISK
Review Completion Date	December 20, 2018
Subject	Evaluation of Need for a REMS
Established Name	Buprenorphine Extended-Release
Trade Name	Brixadi
Name of Applicant	Braeburn Pharmaceuticals Incorporated
Therapeutic Class	Opioid Agonist
Formulation(s)	Long Acting Depot Injection for subcutaneous injection
Proposed Dosing Regimen	Once Weekly and Once Monthly extended-release solution for injection in a pre-filled syringe available in 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg and 128 mg

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary for Brixadi (buprenorphine extended-release injection), a single entity drug-device combination product with buprenorphine base, to ensure the benefits outweigh its risks. In May 2017, Braeburn Pharmaceuticals, Incorporated (Braeburn) submitted a New Drug Application (NDA) 210136 for Brixadi with the proposed indication for the (b) (4) treatment of opioid use disorder (OUD). This application received a Complete Response (CR) on January 19, 2018 and was resubmitted May 23, 2018. The resubmission was not complete and Braeburn was informed of an Incomplete Response on June 22, 2018. They again resubmitted the application on July 12, 2018. This submission is under review in Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

Brixadi is a prefilled syringe of buprenorphine and will be packaged with a needle designed for subcutaneous injection. Braeburn has proposed weekly and monthly dosing formulations, which are to be administered by a healthcare provider. The risks associated with Brixadi are consistent with other opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS). However, the Agency is particularly concerned about the risks of serious harm or death that could result from intravenous (IV) self-administration of Brixadi, if the product is dispensed directly to the patient. Feedback from both the from the REMS Oversight Committee and the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) supported that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of Brixadi outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients.

DRISK communicated what elements would need to be part of the REMS during the previous review cycle.[1] In addition, an Advice Letter was sent on March 14, 2018 providing further details for the REMS Document and materials. The May 23, 2018 NDA resubmission contained the requested REMS Document and materials.

The Applicant's amended final REMS submission received December 17, 2018 has included all the necessary changes communicated on October 23, 2018, November 20, 2018, and December 14, 2018. DRISK finds the Brixadi REMS acceptable and recommends approval of the Brixadi REMS.

[1] Dunn, S. DRISK REMS Review DARRTS January 9, 2018.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits outweigh the risks for Brixadi (buprenorphine extended-release injection), a prefilled syringe single entity drug-device combination product with buprenorphine base. Indivior submitted a New Drug Application (NDA 210136) for Brixadi proposed for the treatment of moderate to severe opioid use disorder (OUD). This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2 Background

2.1 PRODUCT INFORMATION

Brixadi is a prefilled syringe with a modified-release formulation of buprenorphine in a novel FluidCrystal™ technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in Brixadi, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA 2000), codified at 21 U.S.C. 823(g). Brixadi is proposed to provide sustained plasma levels of buprenorphine and is intended for the treatment of opioid use disorder (OUD). Brixadi is designed to be subcutaneously injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Brixadi is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg and 128 mg for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application. The referenced product is Subutex sublingual tablet, NDA 20732. The active ingredient in Brixadi, buprenorphine, is available currently as sublingual tablets and film, buccal film, an implant and as subcutaneous depot injection indicated for the treatment of opioid dependence and used as Medication-Assisted Treatment (MAT), all of which are approved with a REMS. The initial NDA submission did not propose a REMS. Instead, the Applicant proposed that since the product was intended to be administered in healthcare settings by healthcare providers (HCP), it did not need a REMS and the risks could be adequately addressed by other controls, such as a closed distribution. During the course of the first review, the Agency informed the Applicant of a REMS requirement. The complete response letter communicated that a REMS is necessary for Brixadi, if it is approved, to ensure that the benefits of the drug outweigh the risk(s) of serious harm or death that could result from IV self-administration. The REMS must include the following ETASU: healthcare settings and pharmacies that dispense Brixadi must be certified. The REMS must also include an implementation system and a timetable for submission of assessments of the REMS.

2.2 DRISK REVIEWS CONTRIBUTING TO THIS APPLICATION

- Dunn, S. DRISK REMS Review January 9, 2018. DARRTS Reference ID 4204970.
- Dunn, S. DRISK REMS Review October 19, 2018. DARRTS Reference ID 4336931.
- Dunn, S. DRISK REMS Review November 20, 2018. DARRTS Reference ID 4354595.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210136 relevant to this review:

- 05/08/2017: Braeburn submitted NDA 210136; the application did not include a proposed REMS.
- 07/24/2017: The Agency sent an information request (IR) asking the Applicant to further characterize the product's size and consistency after injection and to describe potential consequences of IV injection.
- 07/31/2017: Braeburn responded to the IR above providing data on the size and characteristics of the embolus and provided some limited information on the potential consequences of IV administration. They did not provide specific data to support their predictions of consequences of IV administration.
- 09/19/2017: REMS Oversight Committee meeting was held to discuss NDA 210136.
- 11/01/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 210136.
- 11/10/2017: Braeburn submitted a REMS submission amendment to their NDA. This consisted of a REMS Document only.
- 01/19/2018: Braeburn received a Complete Response Letter. The deficiencies included manufacturing issues and dataset discrepancies.
- 03/14/2018: The Agency provided comments on the proposed REMS for NDA 210136, submitted as part of the primary review cycle, in a General Advice Letter to Braeburn.
- 05/23/2018: Braeburn resubmitted the NDA for review, a proposed REMS was included with the submission; this is the subject of this review.
- 06/22/2018: Braeburn was informed that their submission was an Incomplete Response due to ongoing dataset deficiencies and therefore the Agency did not start the review clock.
- 07/12/2018: Braeburn resubmitted a full application resolving the deficiencies; the REMS was submitted previously on 05/23/2018.
- 10/23/2018: The Agency provided comments to the Applicant on the REMS submitted on 05/23/2018.
- 11/8/2018: Braeburn submitted a REMS amendment based on comments provided by the Agency on 10/23/2018.
- 11/20/2018: The Agency provided comments to the Applicant on the REMS submitted on 11/8/2018.
- 12/11/2018: Braeburn submitted a REMS amendment based on comments provided by the Agency on 11/20/2018.

- 12/14/2018: The Agency provided comments via email to the Applicant on the REMS submitted on 12/11/2018.
- 12/17/2018: Braeburn submitted a REMS amendment based on comments provided by the Agency on 12/14/2018.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Rates of overdose and related deaths continue to have a serious impact on public health; from 1999 to 2016, more than 200,000 people died in the United States from overdoses involving prescription opioids.[2] In addition, opioid analgesic misuse and abuse remains a significant public health crisis contributing to destruction of individuals and families. Overall, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) report that nonmedical use of prescription opioids by adults more than doubled in the U.S. from 2001-2002 to 2012-2013. They also report that the number of people who meet the criteria for prescription opioid addiction has substantially increased during this timeframe as well, with 2.1 million adults reporting symptoms of "nonmedical prescription opioid use disorder."[3] In the face of this public health crisis, new therapies for treatment are necessary.

3.2 Description of Current Treatment Options

Treatment of addiction with methadone is limited to federally regulated Opioid Treatment Programs (OTP). For buprenorphine use in MAT, the Substance Abuse and Mental Health Services Administration (SAMHSA) manages the DATA 2000 in which providers (physicians, nurse practitioners, and physician assistants) that apply and hold waivers can prescribe and/or dispense buprenorphine products for MAT. SAMHSA sets eligibility and certification requirements as well as an interagency notification review processes for providers who apply. Buprenorphine treatment may be prescribed by providers with a DATA 2000 waiver in office practice settings.

Addiction treatment is multifactorial and should address an individual's medical, psychological, social, vocational, and legal problems. It is a long-term process and should include behavioral therapies that

[2] Prescription Opioid Overdose Data. Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/data/overdose.html (accessed 12/12/2018)

[3] NIAAA Press Release on June 22, 2016. Rates of nonmedical prescription opioid use and opioid use disorder double in 10 years. https://www.niaaa.nih.gov/news-events/news-releases/rates-nonmedical-prescription-opioid-use-and-opioid-use-disorder-double-10 (accessed 12/13/2018).

can include counseling which may involve group settings or other family members. MAT is an important part of addiction treatment with OUD.[4]

Table 1 provides a summary of the medications approved by the FDA for treatment of OUD. Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS.

As an injectable depot prefilled syringe, the Brixadi formulation differs significantly from the transmucosal formulations of buprenorphine. Those products are self-administered by patients in their homes and the BTOD REMS is designed to mitigate risks associated with accidental overdose, particularly in children, as well as misuse, and abuse. The BTOD REMS does not have a closed distribution.

There are two approved buprenorphine products that are designed to be administered by a HCP. One of these, Probuphine, is comprised of implantable rods that contain buprenorphine and carries the risks of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of the rods as well as the risks of accidental overdose, misuse and abuse. The other, Sublocade (buprenorphine extended-release injection), is the most similar to Brixadi in terms of risk as it is a depot formulation of buprenorphine in a prefilled syringe designed to be administered by a HCP and was approved with a REMS to mitigate the risk of serious harm or death that could result from IV self-administration. The REMS for Sublocade consists of elements to assure safe use (i.e., healthcare setting certification), implementation system and a timetable for submission for assessments.

Table 1 Summary of currently available FDA-approved drugs for opioid use disorder

Immediate-Release Products			
Generic Name	**Trade Name**	**Applicant**	**Dosage forms**
Buprenorphine/naloxone	Suboxone* (generics only)	Indivior	sublingual tablet
	Suboxone (and generics)	Indivior	sublingual film
	Bunavail (and generics)	Biodelivery Sci Intl	buccal film
	Zubsolv (and generics)	Orexo AB	sublingual tablet
Buprenorphine	Subutex** (generics only)	Indivior	sublingual tablet
Methadone HCl	Methadose (and generics)	Mallinckrodt	oral solution; bulk powder; tablet dispersible tablet

[4] NIDA Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). Principles of Effective Treatment. https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/principles-effective-treatment (accessed 12/13/2018).

Methadone HCl	Dolophine (and generics)	Roxane	tablet; oral concentrate; oral solution
Naltrexone HCl	ReVia (and generics)	Duramed	tablet
Extended-Release Products			
Generic/Chemical Name	**Trade Name**	**Applicant**	**Dosage forms**
Naltrexone HCl	Vivitrol	Alkermes	injectable suspension
Buprenorphine	Probuphine***	Braeburn	subdermal implant
Buprenorphine	Sublocade	Indivior	injectable suspension

*NDA 020733; discontinued in US Market

**NDA 020732; discontinued in US market in 2011

***suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg), requires surgical insertion and removal, and carries a risk of implant migration or expulsion.

Source: Gioia M. Guerrieri, DO, FDA Brixadi Clinical Review Table 3, December 20, 2018

4 Benefit Assessment[5]

Buprenorphine is already approved in other formulations for this indication and this is a 505 (b)(2) application. The efficacy of this formulation, Brixadi, was demonstrated with noninferiority in a Phase 3 study, (HS-11-421) which had 428 outpatient adult males and females with moderate-to-severe OUD. The study was conducted in two phases, weekly (phase 1) then monthly (phase 2), with each phase lasting 12 weeks. Urine was tested weekly in phase 1 and monthly in phase 2. There were also three random urine samples collected during phase 2. The primary efficacy analysis was based on a responder rate that included no evidence of illicit opioids use in urine samples obtained at weeks 10, 11, 12, 13 (last month; phase 1) and urine-negative at weeks 17, 21, 25 (and the three random samples obtained in phase 2). Non-inferiority of Brixadi over an active comparator (Subutex) was established (p = 0.001; with a non-inferiority margin of 10%).

The primary efficacy review was conducted by the statistical reviewer, James Travis, Ph.D., Division of Biometrics II. The Applicant's CR response to the dataset deficiencies impacted some of his supportive analyses (designed to provide understanding the conduct of the study) but did not change Dr. Travis' conclusions of the established efficacy.

[5] Travis, J. FDA Division of Biometrics II Statistical Review and Evaluation of NDA 210136. December 22,2017. DARRTS Reference ID 4199935.

5 Risk Assessment & Safe-Use Conditions[6]

The Safety data review was focused on patients with OUD who received Brixadi. Across all studies in the clinical development program, 729 patients with OUD were exposed to at least one dose. Of those exposures, 604 patients received Brixadi weekly and 408 patients received Brixadi monthly dosing, respectively. Two Phase 3 and three Phase 2 studies comprised the safety review for this product.

The most common AEs occurring in the clinical development were nausea, vomiting, headache, dizziness, pruritus, and injection site reactions. Overall, AEs were consistent with the adverse event profile known to buprenorphine treatment in conjunction with an injectable delivery system (observed injection site reactions were comparable to placebo injections in the clinical development program). There was one death due to motor vehicle accident in the clinical program. The clinical reviewer, Dr. Guerrieri concluded that this death was most likely not related to Brixadi.

The Applicant reported five (2.3%) serious adverse events (SAEs) in the Brixadi group compared with 13 (6.0%) in the Subutex group in Study HS-11-421. In one of the supportive studies, HS-14-499, which was open label and did not have a comparator group, the number of patients who experienced an SAE was 12 (5.3%). No SAE's were reported in the other supportive studies for safety evaluation. SAEs included cardiac (chest pain, tachycardia), headache, tooth abscesses, and injection site pain. The pattern of SAEs did not identify novel systemic findings inconsistent with the known safety profile of buprenorphine. In the review of the updated submission, there was one additional SAE that occurred after the initial database lock where the reviewer considered that Brixadi may have contributed to the events that led to the patient requiring hospitalization and liver failure. However, buprenorphine has been associated with hepatic toxicity, as noted in labeling for sublingual buprenorphine products and if approved will be labeled accordingly. In addition, in this case, several comorbid contributing factors made it difficult to assign causation.

There were no SAEs related to injection site, however, there were two patients that discontinued treatment due to injection site ulcers. Most of the AEs related to injection site were pruritis and pain.

5.1 Potential Serious Risk of Brixadi

The risks associated with Brixadi are consistent with other opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS). However, the Agency is particularly concerned about the risks of serious harm or death that could result from intravenous (IV) self-administration of Brixadi, if the product is dispensed directly to the patient. The Agency has determined that IV injection presents a risk of serious harm or death since Brixadi forms a gel upon contact with body fluids. As a result, potential consequences of IV administration include occlusion, local tissue damage, and thrombo-embolic events, including life-threatening pulmonary emboli. In the clinical development program, the product was administered by healthcare providers in clinical settings and as such, the chance of improper injection as

[6] Guerrieri, G. FDA DAAAP Clinical Reviews for NDA 210136. January 12, 2018 and December 20, 2018. DARRTS ID 4201745.

a medication error was very low. However, once marketed, there is concern that there is a potential for IV administration if the prefilled syringe is provided directly to a patient with OUD.

The Agency is particularly concerned about the risk associated with this product, because it is an injectable form of buprenorphine, available in prefilled syringes with needles attached and designed for subcutaneous use. It is ready to inject and is in a final product configuration that is typically dispensed for outpatient use. There is a potential for abuse and misuse with this product since, given the proposed indication, many patients prescribed this mediation will have a history of IV drug abuse. Fifty percent of subjects in the clinical studies reported history of IV drug use. If Brixadi is injected IV, the doses range from 8 mg to 128 mg and the formulation does not contain naloxone.

Importantly, as IV is not the proposed route of administration, results of IV injection were not studied in the clinical program and serious harm or death may result. The Agency is concerned that potential adverse events (AEs) that may result from IV injection such as tissue damage, embolus, in addition to rapid dissolution resulting in high levels of opioid and respiratory depression.

Overall, the risks associated with IV administration were not well characterized in the clinical program. However, this product will be available in a prefilled syringe with a needle attached and many patients will likely have history of IV drug abuse, therefore the Agency has concerns with potential consequences of IV injection.

As with Sublocade labeling, a product with similar indication, formulation and risk, the Applicant has proposed "Dosage and Administration" labeling language that states that this product is for subcutaneous injection only (b) (4) (b) (4) This is repeated in "Warnings and Precautions" and states "Do not administer intravenously, intramuscularly, or intradermally."

6 Expected Postmarket Use

As an injectable depot formulation, Brixadi could be a potential treatment for patients that have compliance issues or having difficulty taking their daily medications. Based on the clinical program, proposed indication, and proposed locations of administration, it would be likely be prescribed by providers in inpatient settings, OTPs, or by providers in outpatient settings with a DATA 2000 waiver. Some of the clinical settings where patients with OUD would be seen include group practices, independent practices, medical institutions, Department of Defense (DoD) facilities, outpatient clinics, hospitals, Veterans Administration (VA) facilities and OTPs. In summary, the Applicant proposed the following distribution scheme (Figure 1).

Figure 1 Applicant Proposed Distribution Plan of Brixadi

(b) (4)

Source: Braeburn Supporting Document

The proposed distribution scheme could ensure that Brixadi is dispensed (b) (4)

(b) (4)

7 Discussion of Need for a REMS

The Clinical Reviewer, Dr. Guerrieri, recommends approval of Brixadi with a REMS based on the efficacy and safety information currently available. All approved buprenorphine products for opioid dependence are approved with a REMS. However, the risks mitigated in the REMS for the products are not the same. As discussed in Section 3.2, Probuphine has risks associated with migration of the implant. Transmucosal buprenorphine products for opioid dependence (Suboxone, Subutex, Bunavail, Zubsolv and generics) are intended for the patient to take at home and risks are like that seen with other opioids such as misuse, overdose and respiratory depression. The product formulation for Brixadi differs from the other buprenorphine products indicated for the treatment of opioid dependence and contributes to a different risk profile, except for Sublocade which is a similar product. Unlike transmucosal buprenorphine products, Brixadi was not developed as a take-home formulation; if a HCP administers the depot injection as proposed, studied and indicated, misuse and overdose by the patient are not likely to occur. In addition, the risk of accidental exposure to children is reduced because the product is not stored in the home.

The injection site reactions when injected subcutaneously were not concerning as discussed in Section 5. However, Brixadi is is an opioid agonist in prefilled injectable syringes with needles attached, it is ready to inject, intended for use in a population with known opioid dependence. As noted by the Applicant, there is a potential risk for abuse and misuse with this product since, given the proposed indication, many patients prescribed this mediation will have a history of IV drug abuse and the product doses are very high and the formulation does not include naloxone. Because Brixadi forms a gel upon contact with body fluids the Agency is concerned about the potential AEs that may result from IV injection (i.e. embolus, rapid dissolution resulting in high levels of opioid).

During the first review cycle, the Applicant was asked to provide information on the potential adverse events that could occur with an IV injection. They responded that injection leads to immediate formation of a macroscopic gel upon injection into any aqueous space. Although they stated probability of portions of the gel breaking off into fragments is unlikely and the risk of distant embolism was considered "remote" they had no evidence to support this and did not provide any with their response. The injected depot was described as large as 1 cm in size. Overall the Applicant did not characterize the risks from IV injection well and the Agency remained concerned about the potential downstream AEs from IV injection.

Brixadi route of administration is similar to other injectable depot and subcutaneous products dispensed for outpatient use. The Agency is very concerned that since dispensing subcutaneous and injectable depot medication to patients occurs in practice, Brixadi may be dispensed to patients. Due to the aforementioned risks, a REMS is necessary to ensure the benefits outweigh the risks of Brixadi and ensure that it is administered by a HCP. The drug was administered by the HCP in the clinical trials and no additional data has been provided to support alternative options for administration. Based on the available data and the potential risks, the Agency has determined that a REMS is necessary to mitigate the risk of serious harm or death that could result from intravenous self-administration by patient, by ensuring healthcare settings and pharmacies are certified and only dispense Brixadi directly to a healthcare provider. These healthcare settings and pharmacies will need to ensure that appropriate safety measures are in place so the product is administered by a HCP. The REMS would ensure that Brixadi is used and administered by a HCP; however, HCP compliance with the REMS requirements are key to ensuring that the product is administered by a HCP and not dispensed directly to patient.

DRISK held several teleconferences with healthcare providers and administrators from American Society of Health-System Pharmacists (ASHP) including representation from the Cleveland Clinic, Indian Health Service (IHS) and Veteran's Administration (VA) to gain a better understanding how this type of product would move through their medication-use system. We were particularly interested in what policies and processes are currently in place for procurement, storage and distribution within these healthcare systems. These took place on the following dates:

- 10/16/2017: DRISK held a teleconference with ASHP and a representative from the Cleveland Clinic.
- 10/18/2017: DRISK held a teleconference with IHS healthcare representatives.
- 10/20/2017: DRISK held a teleconference with VA healthcare representatives.

The Agency was interested in identifying possible gaps where a healthcare system or site may dispense this type of product directly to patients. The teleconferences were instrumental in recognizing the differences between these hospitals and healthcare settings and their clinics and pharmacies. DRISK notes that in some healthcare settings there is a centralized pharmacy for inpatient and outpatient and other systems may have use a separate pathway for procurement of drugs for out pharmacies. The Agency has determined that all sites receiving product from the wholesaler/distributor should be certified and enrolled. This will ensure that in each case, under the various healthcare settings, there will

be processes and procedures in place to ensure that dispensing staff are aware Brixadi should be administered by a HCP and cannot be dispensed directly to patients.

As Brixadi is administered as a monthly injection it removes the need for daily doses of MAT and therefore could be a useful addition to helping patients with OUD. The PDAC and DSaRM AC on 11/1/2018 overall supported approval of the product during the first review cycle. However, they unanimously voted not to approve all the proposed doses. They largely were in favor of approval but only for some of the doses (vote was yes to all doses 0, yes to some doses 17, no to all doses 3). The Agency also did not feel that there was enough data to support the 160 mg dose. Of note, the Applicant did not propose this dose when they resubmitted in 2018 (where they also addressed the main deficiency having to do with datasets). The AC supported a REMS for Brixadi, but expressed concern about limiting access in rural settings if the product is not available in retail pharmacies. Since Brixadi is intended to be administered by HCP and the product should not be given to patients, the Agency is requiring certification of all pharmacies and healthcare settings that dispense Brixadi. However, individual practitioners that have a DATA 2000 waiver do not need to certify, if they are ordering Brixadi for a named patient through a certified pharmacy.

DRISK has determined that HCP training and patient education are not necessary elements to support the goal. HCPs in an office setting must obtain a DATA 2000 waiver to prescribe buprenorphine for MAT outside of OTPs settings, therefore they are already receiving required training on treating OUD with buprenorphine. Due to the depot, injectable formulation of Brixadi, this formulation of buprenorphine has risks that differ from most of the other buprenorphine products for MAT. As discussed, most of these products are taken and stored at home and as a result are more susceptible to misuse, abuse and accidental overdose. Respiratory depression and NOWS are risks that increase with opioid medications that handled by patients and stored in their homes for use. Since this product, once administered, is not handled by patients, the Appropriate Use Checklist and HCP Brochure, which provide guidance on counseling patients on these risks, are not needed to support the goal of the Brixadi REMS. The REMS for Probuphine is designed to mitigate risks associated with implant formulation. This risk is also not applicable to Brixadi.

The Agency's REMS includes the necessary requirements; thoughtful consideration was given to minimizing additional burden on healthcare providers and patients. For this reason, the Brixadi REMS includes a one-time healthcare setting and pharmacy certification and as part of the certification these entities are required to put policies and procedures in place to ensure that Brixadi is not dispensed directly to patients and train all relevant staff involved in dispensing that the drug must be dispensed directly to a healthcare provider for administration by a healthcare provider, and the drug must not be dispensed to the patient. This REMS program is similar to the Sublocade REMS, which was approved on November 30, 2017 for the same risk.

The rationale, ETASU, goals and materials were communicated to the Applicant prior to the resubmission of the REMS in May 2018.

8 Risk Management Activities Proposed by the Applicant

Proposed labeling includes a "Warning and Precautions" section addresses respiratory depression, NOWS and hepatic events consistent with other labeling for buprenorphine. The "Use in Specific Populations" section also addresses use in patients with hepatic impairment. The proposed "Drug Interactions" section includes a caution statement for use with benzodiazepines and CNS depressants.

In their initial NDA submission, the Applicant did not propose a REMS citing that there were no identified safety concerns during the clinical program or previously identified with Brixadi to warrant a REMS given the expected use in healthcare settings. Since the proposed closed distribution could not be ensured and the Agency was concerned about IV self-administration if the drug is dispensed directly to patients, the Applicant was informed that a REMS would be needed. They were advised on the ETASU and components that would be required during the previous review cycle and prior to resubmission. The resubmission in May 2018 contained the requested REMS proposal (the next resubmission of the NDA in June 2018 did not contain another REMS proposal) and during the second review cycle the materials were refined via communication with the Applicant. As such, the final REMS proposal is presented here; the REMS Document, goal and materials have been agreed upon.

8.1 REVIEW OF APPLICANT'S REMS

8.1.1 REMS Goals

The proposed REMS goal is to:

The goal of the Brixadi REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:

- Ensuring healthcare settings and pharmacies are certified and only dispense BRIXADI directly to a healthcare provider for administration by a healthcare provider.

8.1.2 REMS Requirements-ETASU

As noted, the Agency has determined that all sites receiving product from the wholesaler/distributor should be certified and enrolled. This will ensure that in each case, under the various healthcare settings, there will be processes and procedures in place to ensure that dispensing staff are aware Brixadi should be administered by a HCP and cannot be given directly to patients. To assist healthcare providers with understanding the requirements of the REMS, the Agency is requiring a Fact Sheet that explains how obtain Brixadi for patients in various settings. The Agency is also requiring an enrollment form for pharmacies and healthcare settings to enable certification in the REMS. The Applicant submitted the required materials with the necessary information. These include:

- Brixadi REMS Fact Sheet—this material details the process for obtaining Brixadi.
  - Any pharmacy that dispenses BRIXADI as well as any healthcare setting (including a prescriber's office) that purchases Brixadi from a distributor must be certified prior to dispensing/purchasing.
  - Prescriber offices that only order Brixadi from a certified pharmacy for a specific patient are exempt from certification.

- [redacted] (b) (4) prescribers can order from a certified pharmacy for a named patient or they can certify their healthcare setting if they plan to administer it.

- Dear Healthcare Provider Letter informing them about the REMS
- Healthcare Setting and Pharmacy Enrollment Form
- REMS Website

These materials were submitted as requested and contain the required information.

8.1.3 Brixadi Supporting Document and REMS Assessment Plan

The Supporting Document discusses the operations of the program including details for the distribution scheme. The final assessment plan includes but is not limited to the following requirements.

The REMS Assessment Plan for Brixadi will include, but is not limited to, the following metrics for the reporting period and cumulatively:

[redacted] (b) (4)

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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.

The BRIXADI REMS will undergo periodic review to evaluate the effectiveness of the strategies and educational tools in accomplishing the goals and objectives of the REMS. Appropriate revisions to the REMS will be proposed based on these evaluations.

9 Conclusion & Recommendations

The Agency is concerned that intravenous injection could result in serious harm or death as Brixadi forms a gel upon contact with body fluids. There is concern with the risk of harm or death that could result from IV self-administration of Brixadi by a patient. DRISK is recommending a REMS consisting of elements to assure safe use to ensure that the benefits outweigh the risks. Certifying healthcare settings that order and receive Brixadi from the wholesaler/distributor will help to ensure that all the dispensing sites have policies and procedures in place to ensure that it is only dispensed directly to a healthcare provider for administration by a healthcare provider.

The Applicant's amended REMS submission received December 17, 2018 has included all the necessary changes communicated on October 23, November 20 and December 14, 2018. DRISK is recommending approval of the Brixadi REMS.

10 Appendices

1. Brixadi REMS Document
2. Brixadi REMS Program Healthcare Setting and Pharmacy Enrollment Form
3. Brixadi REMS Program Dear Healthcare Provider Letter
4. Brixadi REMS Program Fact Sheet: How to Obtain Brixadi
5. Brixadi REMS Website Screenshots

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	November 27, 2018
Reviewer(s):	Somya Dunn, M.D., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H., Health Communications Analyst, DRISK
Team Leader:	Selena Ready, Pharm.D, DRISK
Division Director:	Cynthia LaCivita, Pharm.D, DRISK
Drug Name(s):	Buprenorphine extended-release
Therapeutic Class:	Opioid Partial Agonist
Dosage and Route:	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) (b) (4) subcutaneous injection
Application Type/Number:	NDA 210136
OSE RCM #:	2017-1447

1 INTRODUCTION

The purpose of this review by the Division of Risk Management (DRISK) is to provide an evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Brixadi a single entity drug-device combination product with a buprenorphine base. In May 2017, Braeburn Pharmaceuticals, Incorporated (Braeburn) submitted a New Drug Application (NDA) 210136 for Brixadi with the proposed indication for the (b) (4) (b) (4) treatment of opioid use disorder (OUD). This application received a Complete Response (CR) on January 19, 2018 and was resubmitted May 23, 2018. Braeburn was informed of an Incomplete Response on June 22, 2018 and resubmitted a full application on July 12, 2018. This submission is under review in Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

Brixadi is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection. Braeburn has proposed weekly and monthly dosing formulations, which are to be administered by a healthcare provider. The risks associated with Brixadi are consistent with other opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS). However, the Agency is particularly concerned about the risks of serious harm or death that could result from intravenous (IV) self-administration of Brixadi, if the product is dispensed directly to the patient.

DRISK determined, based on feedback on Brixadi from the REMS Oversight Committee and the November 1, 2017, Psychopharmacologic Drugs Advisory Committee (PDAC) , and Drug Safety & Risk Management Advisory Committee (DSARM), that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of Brixadi outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients.[1] The original submission in May 2017 did not contain a REMS. The REMS proposed in the May 23, 2018 submission consists of elements to assure safe use (i.e., healthcare setting and pharmacies that dispense Brixadi must be certified), implementation system, a Medication Guide and a timetable for submission for assessments.

1.1 BACKGROUND

Brixadi is a single entity drug-device combination product with a modified-release formulation of buprenorphine in a novel FluidCrystal™ technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in Brixadi, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA), codified at 21 U.S.C. 823(g). Brixadi is proposed to provide sustained

[1] Dunn, S., DRISK REMS Review DARRTS January 9, 2018.

plasma levels of buprenorphine and is intended for the treatment of opioid use disorder (OUD). Brixadi is designed to be subcutaneously injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Brixadi is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Brixadi, buprenorphine, is available currently as sublingual tablets and film, buccal film and as an implant indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS.

As an injectable depot device, the Brixadi formulation differs significantly from the sublingual and buccal formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children, as well as misuse, and abuse. There are two approved products that are designed to be administered by a healthcare provider (HCP). One of these, Probuphine, is comprised of implantable rods that contain buprenorphine and carries the risks of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of the rods as well as the risks of accidental overdose, misuse and abuse. The other, Sublocade, is the most similar to Brixadi in terms of risk as it is a depot formulation of buprenorphine designed to be administered by a HCP and required a REMS to mitigate the risk of serious harm or death that could result from IV self-administration. The REMS for Sublocade consists of elements to assure safe use (i.e., healthcare setting certification), implementation system and a timetable for submission for assessments.

The Agency is particularly concerned about the risk associated with this product, because it is an injectable form of buprenorphine and will be available in prefilled syringes with needles attached. It is ready to inject and easier to inject than other formulations, and is in a final product configuration that is typically dispensed for outpatient use. If Brixadi is injected IV, the doses range from 8 mg (b) (4) and the formulation does not contain naloxone. There is a potential for abuse and misuse with this product since, given the proposed indication, many patients prescribed this mediation will have a history of IV drug abuse. Fifty percent of subjects in the clinical studies reported history of IV drug use. Importantly, as IV is not the proposed route of administration, results of IV injection were not studied in the clinical program and serious harm or death may result. The Agency is concerned that potential adverse events (AEs) that may result from IV injection such as tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression.

The complete response letter communicated that a REMS is necessary for Brixadi, if it is approved, to ensure that the benefits of the drug outweigh the risk(s) of serious harm or death that could result from intravenous (IV) self-administration. The REMS must

include the following ETASU: healthcare settings and pharmacies that dispense Brixadi must be certified. The REMS must also include an implementation system and a timetable for submission of assessments of the REMS.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210136 relevant to this review:

- 05/08/2017: Braeburn submitted NDA 210136; the application did not include a proposed REMS.
- 09/19/2017: REMS Oversight Committee meeting was held to discuss NDA 210136.
- 11/01/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 210136.
- 11/10/2017: Braeburn submitted a REMS submission amendment to their NDA. This consisted of a REMS Document only.
- 01/19/2018: Braeburn received a Complete Response Letter.
- 03/14/2018: The Agency provided comments on the proposed REMS for NDA 210136, submitted as part of the primary review cycle, in a General Advice Letter to Braeburn.
- 05/23/2018: Braeburn resubmitted the NDA for review, a proposed REMS was included with the submission; this is the subject of this review.
- 06/22/2018: Braeburn was informed that their submission was an Incomplete Response due to ongoing dataset deficiencies and therefore the Agency did not start the review clock.
- 07/12/2018: Braeburn resubmitted a full application, the REMS for this application was submitted previously on 05/23/2018.
- 10/23/2018: The Agency provided comments to the Applicant on the REMS submitted on 05/23/2018.
- 11/8/2018: Braeburn submitted a REMS amendment based on comments provided by the Agency on 10/23/2018; this is the subject of this review.

2 DRISK REVIEWS CONTRIBUTING TO THE REVIEW OF THIS APPLICATION

- Dunn, S. DRISK REMS Review DARRTS, January 9, 2018.
- Dunn, S. DRISK REMS Review DARRTS, October 19, 2018

3 MATERIALS REVIEWED

- Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for Brixadi, submitted December 13, 2017 (Seq. No. 0066)

- Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for Brixadi, submitted May 23, 2018 (Seq. No. 0079)
- Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for Brixadi, submitted November 8, 2018 (Seq. No. 0094)

4 SUMMARY OF APPLICANT'S REMS SUBMISSION AND DRISK COMMENTS

4.1 ELEMENTS TO ASSURE SAFE USE

4.1.1 REMS DOCUMENT

The Applicant did not propose any substantive edits and accepted all the edits provided by the Agency in October.

Reviewer Comment: The proposed REMS Document is acceptable.

4.1.2 REMS SUPPORTING DOCUMENT

In Agency comments provided on October 23, we asked the Applicant to expand on their plan for distribution and display their distribution scheme with a flow diagram. They did make these changes.

Reviewer Comments: As proposed in the SD, the distribution plan is sufficient to ensure the product is sent only to certified healthcare settings and certified pharmacies. The Agency is reviewing the proposed Assessment Plan and will provide comments after the next submission.

4.1.3 BRIXADI REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM

The only changes proposed by the Applicant were those to update addresses and phone numbers.

Reviewer Comments: The proposed changes are acceptable. However, the Applicant needs to make some changes to font color. See the attached pdf bubble comments version.

4.1.4 BRIXADI REMS PROGRAM FACT SHEET

The only changes proposed by the Applicant were those to update phone numbers.

Reviewer Comments: The proposed changes are acceptable. However, the Applicant needs to make additional changes to font color and formatting to improve readability. See the attached pdf bubble comments version.

4.1.5 DEAR HEALTHCARE PROVIDER LETTERS

The Applicant made changes to update addresses and phone numbers.

Reviewer Comments: The proposed changes are acceptable. However, the Applicant needs to make additional changes to font color and formatting to improve readability. They also need to replace the word (b) (4) *with "restricted" when referring to the REMS program. See the attached pdf bubble comments version.*

4.1.6 BRIXADI PROGRAM WEBSITE

The Applicant made changes to update the addresses and phone numbers.

Reviewer Comments: *The Applicant needs to make additional changes to font color and formatting to improve readability. They also need to remove the remaining references to* (b) (4) *See the attached pdf bubble comments version.*

5 OFFICE OF PRESCRIPTION AND DRUG PROMOTION CONSULT

The Office of Prescription Drug Promotion (OPDP) was consulted on May 31, 2018. They received the REMS materials from DRISK on November 13, 2018. Nima Osserah, OPDP reviewer entered his review into DARRTS on November 20, 2018.

The Division of Risk Management (DRISK) considered OPDP's recommendations and noted OPDP's concerns. DRISK agreed with OPDP's comments and agree that the Applicant needs to align the Indication/Use statement on the REMS website with text from the final Brixadi PI.

6 DISCUSSION AND CONCLUSIONS

The original NDA submission for Brixadi received a Complete Response[2] and the NDA was resubmitted in July 2018. As discussed in the previous DRISK REMS Review of the original REMS submission, dated January 9, 2018, the Agency determined that a REMS with ETASU is necessary to ensure the benefits of Brixadi outweigh its risk of serious harm or death that could result from intravenous (IV) self-administration. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients.

On November 8, 2018, Braeburn submitted a REMS amendment in response to comments provided by the Agency on October 23, 2018. DRISK determined that additional changes to the materials are necessary. The Applicant must continue to align all REMS materials with the REMS Document and the Prescribing Information, including the boxed warning, indication, and storage requirements language.

7 COMMENTS FOR THE SPONSOR

The Agency reviewed the REMS amendment submitted on November 8, 2018 and has accepted all tracked changes proposed in the following materials. Refer to the specific attachments for additional comments and edits.

REMS Document
No changes are needed.

REMS Supporting Document
The Agency is reviewing the proposed Assessment Plan and will provide comments after the next submission.

Note additional Agency comments on the attached pdf versions of these materials:

- ***Brixadi REMS Healthcare Setting and Pharmacy Enrollment Form***
- ***Brixadi REMS Fact Sheet: How to Obtain Brixadi***
- ***Brixadi REMS Letter for Healthcare Settings and Pharmacies***
- ***Brixadi REMS Website Screenshots:*** Align the online enrollment content of the website with the actual enrollment form. Note other comments on the website screenshots.

General Comments:
- Use a darker font for the general text in the REMS materials.
- Continue to ensure that all content is consistent across all the REMS materials and website.
- Continue to align all REMS materials with the REMS Document and the Prescribing Information, including the boxed warning, indication, and storage requirements language. This content in the final REMS must match the final label.

Resubmission Instructions:

Submit the materials by 12/10/18. Align with updated labeling, note that additional changes may be required to align with final labeling. Only submit word versions with tracked changes if there are proposed edits. *Otherwise, accept all changes and submit all the materials.*

The next submission via email and to the Gateway should include Clean MS Word, Tracked MS Word (if needed), and final formatted versions of the following six documents. If these are in final form, we also need pdf versions and a compiled version that does not include the REMS Supporting Document. Changes suggested by the Agency to the pdf versions of the materials must also be reflected in the clean MS Word versions.

- ***Brixadi REMS Document***
- ***Brixadi REMS Supporting Document***
- ***Brixadi REMS Healthcare Setting and Pharmacy Enrollment Form***
- ***Brixadi REMS Letter for Healthcare Settings and Pharmacies***
- ***Brixadi REMS Fact Sheet: How to Obtain Brixadi***
- ***Brixadi REMS Website Screenshots***

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/s/

SOMYA V DUNN
11/27/2018

SELENA D READY
11/27/2018

CYNTHIA L LACIVITA
11/28/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	October 18, 2018
Reviewer(s):	Somya Dunn, M.D., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H., Health Communications Analyst, DRISK
Team Leader:	Selena Ready, Pharm.D, DRISK
Division Director:	Cynthia LaCivita, Pharm.D, DRISK
Drug Name(s):	Buprenorphine extended-release
Therapeutic Class:	Opioid Partial Agonist
Dosage and Route:	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) (b) (4) subcutaneous injection
Application Type/Number:	NDA 210136
OSE RCM #:	2017-1447

1 INTRODUCTION

The purpose of this review by the Division of Risk Management(DRISK) is to provide an evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Brixadi a single entity drug-device combination product with a buprenorphine base. In May 2017, Braeburn Pharmaceuticals, Incorporated (Braeburn) submitted a New Drug Application (NDA) 210136 for Brixadi with the proposed indication for the (b) (4) (b) (4) treatment of opioid use disorder (OUD). This application received a Complete Response (CR) on January 19, 2018 and was resubmitted May 23, 2018. Braeburn was informed of an Incomplete Response on June 22, 2018 and resubmitted a full application on July 12, 2018. This submission is under review in Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

Brixadi is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection. Braeburn has proposed weekly and monthly dosing formulations, which are to be administered by a healthcare provider. The risks associated with Brixadi are consistent with other opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS). However, the Agency is particularly concerned about the risks of serious harm or death that could result from intravenous (IV) self-administration of Brixadi, if the product is dispensed directly to the patient.

DRISK determined, based on feedback from the REMS Oversight Committee and the Brixadi Advisory Committee, that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of Brixadi outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients.[1] The original submission in May 2017 did not contain a REMS. The REMS proposed in the May 23, 2018 submission consists of elements to assure safe use (i.e., healthcare setting and pharmacies that dispense Brixadi must be certified), implementation system, a Medication Guide and a timetable for submission for assessments.

1.1 BACKGROUND

Brixadi is a single entity drug-device combination product with a modified-release formulation of buprenorphine in a novel FluidCrystal™ technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in Brixadi, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA), codified at 21 U.S.C. 823(g). Brixadi is proposed to provide sustained plasma levels of buprenorphine and is intended for the treatment of opioid use disorder

[1] Dunn, S., DRISK REMS Review DARRTS January 9, 2018.

(OUD). Brixadi is designed to be subcutaneously injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Brixadi is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Brixadi, buprenorphine, is available currently as sublingual tablets and film, buccal film and as an implant indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS.

As an injectable depot device, the Brixadi formulation differs significantly from the sublingual and buccal formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children, as well as misuse, and abuse. There are two approved products that are designed to be administered by a healthcare provider (HCP). One of these, Probuphine, is comprised of implantable rods that contain buprenorphine and carries the risks of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of the rods as well as the risks of accidental overdose, misuse and abuse. The other, Sublocade is the most similar to Brixadi in terms of risk as it is a depot formulation of buprenorphine designed to be administered by a HCP and required a REMS to mitigate the risk of serious harm or death that could result from IV self-administration. The REMS for Sublocade consists of elements to assure safe use (i.e., healthcare setting certification), implementation system and a timetable for submission for assessments.

The Agency is particularly concerned about the risk associated with this product, because it is an injectable form of buprenorphine and will be available in prefilled syringes with needles attached. It is ready to inject and easier to inject than other formulations, and is in a final product configuration that is typically dispensed for outpatient use. If Brixadi is injected IV, the doses range from 8 mg (b) (4) and the formulation does not contain naloxone. There is a potential for abuse and misuse with this product since, given the proposed indication, many patients prescribed this mediation will have a history of IV drug abuse. Fifty percent of subjects in the clinical studies reported history of IV drug use. Importantly, as IV is not the proposed route of administration, results of IV injection were not studied in the clinical program and serious harm or death may result. The Agency is concerned that potential adverse events (AEs) that may result from IV injection such as tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression.

The complete response letter, communicated that a REMS is necessary for Brixadi if it is approved, to ensure that the benefits of the drug outweigh the risk(s) of serious harm or death that could result from intravenous (IV) self-administration. The REMS must include the following ETASU: healthcare settings and pharmacies that dispense

BRIXADI must be certified. The REMS must also include an implementation system and a timetable for submission of assessments of the REMS.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210136 relevant to this review:

- 05/08/2017: Braeburn submitted NDA 210136; the application did not include a proposed REMS.
- 09/19/2017: REMS Oversight Committee meeting was held to discuss NDA 210136.
- 11/01/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 210136.
- 11/10/2017: Braeburn submitted a REMS submission amendment to their NDA. This consisted of a REMS Document only.
- 01/19/2018: Braeburn received a Complete Response Letter.
- 03/14/2018: The Agency provided comments on the proposed REMS for NDA 210136, submitted as part of the primary review cycle, in a General Advice Letter to Braeburn.
- 05/23/2018: Braeburn resubmitted the NDA for review, a proposed REMS was included with the submission; this is the subject of this review.
- 06/22/2018: Braeburn was informed that their submission was an Incomplete Response due to ongoing dataset deficiencies and therefore the Agency did not start the review clock.
- 07/12/2018: Braeburn resubmitted a full application, the REMS for this application was submitted previously on 05/23/2018.

2 DRISK REVIEWS CONTRIBUTING TO THE REVIEW OF THIS APPLICATION

- Dunn, S. DRISK REMS Review DARRTS, January 9, 2018.

3 MATERIALS REVIEWED

- Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for Brixadi, submitted December 13, 2017 (Seq. No. 0066)
- Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for Brixadi, submitted May 23, 2018 (Seq. No. 0079)

4 SUMMARY OF APPLICANT'S REMS SUBMISSION AND DRISK COMMENTS

4.1 ELEMENTS TO ASSURE SAFE USE

4.1.1 REMS DOCUMENT

In October of 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry[2] which provides updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug products. Because this is a new guidance, DRISK provided a draft REMS Document populated with the proposed Brixadi REMS for their review on 12/6/2017. Braeburn submitted the draft REMS Document with edits.

Reviewer Comment

The Agency cannot accept the most of the edits made by the Applicant. For consistency and standardization with other REMS Documents, the Agency is declining some of the proposed changes to the REMS document. See redlined version.

4.1.2 REMS SUPPORTING DOCUMENT

The Supporting Document describes Braeburn's proposed distribution plan and proposed operations. It also incorporates language from the proposed label and REMS Document.

Reviewer Comment

In the Supporting Document, Braeburn should provide additional details that clarifies the steps and processes for the distribution scheme and implementation of their proposed REMS program. For example, a flow diagram on their distribution plan to differing distribution sites may be helpful. Therefore, Braeburn will need to provide further details on their proposed operations. In addition, Braeburn will need to align the Supporting Document with the current labeling and the REMS Document as they are being updated during the review of the application. The Applicant has referred to pharmacies and distributors as "specialty." This is acceptable when they discuss their operations in the SD, but should not be mentioned as a REMS requirement as this is not a requirement in the REMS; this is true for all REMS materials (further listed in this section). See redlined version.

4.1.3 BRIXADI REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM

The Applicant received a templated draft Healthcare Setting and Pharmacy Enrollment Form on 12/6/2017. Braeburn submitted the proposed Enrollment Form with edits to this material.

Reviewer Comment

In general, most of the edits are acceptable. However, Braeburn will need to make additional adjustments to this form, see redlined version.

4.1.4 BRIXADI REMS PROGRAM FACT SHEET

[2] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

At the 12/5/2017 teleconference, DRISK informed the Sponsor that the Fact Sheet should describe how various stakeholders, such as DATA 2000 waivered providers, can obtain Brixadi. The Applicant resubmitted this material with minimal edits.

Reviewer Comment

Some of the edits are acceptable. However, Braeburn will need to make adjustments to this form, see redlined version.

4.1.5 DEAR HEALTHCARE PROVIDER LETTERS

On 12/6/2017, DRISK provided templated letters to Braeburn and the proposed letters were resubmitted with minimal edits.

Reviewer Comment

Some of the edits are acceptable. However, Braeburn will need to make additional adjustments to this form, see redlined version.

4.1.6 BRIXADI PROGRAM WEBSITE

The website screenshots were submitted with minimal edits.

Reviewer Comment

Some of the edits are acceptable. However, Braeburn will need to make additional adjustments to this form, see redlined version.

5 DISCUSSION AND CONCLUSIONS

The original NDA submission for Brixadi received a Complete Response[3] and the NDA was resubmitted in July 2018. As discussed in the previous DRISK REMS Review dated January 9, 2018, of the original REMS submission, the Agency determined that a REMS with ETASU is necessary to ensure the benefits of Brixadi outweigh its risk of serious harm or death that could result from intravenous (IV) self-administration. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Brixadi to ensure that it is administered by healthcare providers and not dispensed directly to patients.

On May 23, 2018, Braeburn submitted a proposed REMS that consists of ETASU (healthcare setting and pharmacies that dispense Brixadi must be certified), implementation system, a Medication Guide and a timetable for submission for assessments. This submission incorporated the comments previously provided by the Agency in a General Advice letter, as well as other changes.

In general, DRISK agrees with the proposed REMS. However, additional changes to the materials and REMS Document are necessary.

6 COMMENTS FOR THE SPONSOR

The Agency has reviewed the REMS materials submitted on May 23, 2018 and has made new track changes and comments to the clean versions of the REMS materials and additional track changes and comments to the track change versions of the REMS Document and REMS Supporting Document.

REMS Document

For consistency and standardization purposes, the Agency cannot accept most edits. Although we requested you remove the word "Program" from the materials, it should stay in the REMS Document. See redlined version.

REMS Supporting Document

Provide additional details that clarifies the steps and processes for the distribution scheme and implementation of the proposed REMS program. For example, include a flow diagram on the distribution plan to differing distribution sites. We need further details on the proposed operations. In addition, align the Supporting Document with the current labeling and the REMS Document as they are being updated during the review of the application.

Referring to pharmacies and distributors (b) (4) is acceptable when discussing operations in the SD if that is how you have chosen to implement certain requirements; however, it is not a REMS requirement and should not be referred to as such. The use of the word (b) (4) to describe pharmacies must not be included as such in the materials. Include your noncompliance protocol and audit plan. See redlined version.

The Agency has accepted most track changes proposed by you in the following materials. Please see the clean versions for additional revisions and comments from the Agency:

Brixadi REMS Program Healthcare (b) (4) ***Form***
Brixadi REMS Program Fact Sheet: How to Obtain Brixadi
Brixadi REMS Program Letter for Healthcare Settings and Pharmacies
Brixadi REMS Program Website Home Page Content: In your next submission, provide website screenshots for the Agency's review - showing all content and functionality of the website, including the online enrollment process, footers, links, and the navigation bar.

General Comments:

- Continue to ensure that all content is consistent across all of the REMS materials and website.
- Continue to align all REMS materials with the REMS Document and the Prescribing Information, including the boxed warning, indication, and storage requirements language. It is acceptable to wait to update these sections in the REMS materials until after the prescribing information is more final. This content in the final REMS must match the final label.

Resubmission Instructions:

Submit the following revised REMS materials to your application by COB, November 9, 2018. If you are proposing any edits, you will need to include tracked changes versions. Otherwise, accept all changes and submit final versions of the materials, there still may be some changes needed to align with labeling and a final set of revised materials can be resent if this occurs.

The next submission via email and to the Gateway should include Clean MS Word, Tracked MS Word (if needed), and final formatted versions of the following six documents. If these are in final form, we also need pdf versions and a compiled version that does not include the REMS Supporting Document:

- ***Brixadi REMS Document***
- ***Brixadi REMS Supporting Document***
- ***Brixadi REMS Program Healthcare Setting and Pharmacy Enrollment Form:***
- ***Brixadi REMS Program Letter for Healthcare Settings and Pharmacies***
- ***Brixadi REMS Program Fact Sheet: How to Obtain Brixadi***
- ***Brixadi REMS Program Website Home Page Screenshots***

ATTACHMENTS

1. Brixadi REMS Document
2. Brixadi Supporting Document (email only)
3. Brixadi Program Healthcare Setting and Pharmacy Enrollment Form
4. Brixadi Program Dear Healthcare Provider Letter
5. Brixadi Program Fact Sheet: How to Obtain Brixadi
6. Brixadi Website Content

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/s/

SOMYA V DUNN
10/18/2018

SELENA D READY
10/18/2018

CYNTHIA L LACIVITA
10/19/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	January 9, 2018
Reviewer(s):	Somya Dunn, M.D., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H., Health Communications Analyst, DRISK
Team Leader:	Selena Ready, Pharm.D, DRISK
Division Director:	Cynthia LaCivita, Pharm.D, DRISK
Drug Name(s):	Buprenorphine extended-release
Therapeutic Class:	Opioid Partial Agonist
Dosage and Route:	8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg (b) (4) (b) (4) subcutaneous injection
Application Type/Number:	NDA 210136
OSE RCM #:	2017-1447

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on REMS materials included in the proposed risk evaluation and mitigation strategy (REMS) for CAM2038, a single entity drug-device combination product with buprenorphine base. In May 2017, Braeburn Pharmaceuticals, Incorporated (Braeburn) submitted a New Drug Application (NDA) 210136 for CAM2038 with the proposed indication for the (b) (4) treatment of opioid use disorder (OUD). This application is under review in Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

CAM2038 is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection. Braeburn has proposed weekly and monthly dosing formulations, which are to be administered by a healthcare provider. The risks associated with CAM2038 are consistent with other opioids, such as respiratory depression and neonatal opioid withdrawal syndrome (NOWS). However, the Agency is particularly concerned about the risks of serious harm or death that could result from intravenous (IV) self-administration of CAM2038, if the product is dispensed directly to the patient.

DRISK determined, based on feedback from the REMS Oversight Committee and the CAM2038 Advisory Committee, that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of CAM2038 outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense CAM2038 to ensure that it is administered by healthcare providers and not dispensed directly to patients. The Sponsor's original NDA submission did not contain a REMS. However, they submitted an amendment to their NDA that included a proposed REMS to include a Medication Guide, ETASU, an implementation system, and a timetable for submission of assessments.

1.1 BACKGROUND

CAM2038 is a single entity drug-device combination product with a modified-release formulation of buprenorphine in a novel FluidCrystal™ technology designed for subcutaneous administration by a healthcare provider. Buprenorphine, the active ingredient in CAM2038, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981 and is a Schedule III narcotic under the Controlled Substances Act and prescription use of this product is limited under the Drug Addiction Treatment Act of 2000 (DATA), codified at 21 U.S.C. 823(g). CAM2038 is proposed to provide sustained plasma levels of buprenorphine and is intended for the treatment of opioid use disorder (OUD). CAM2038 is designed to be subcutaneously injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. CAM2038 is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Braeburn proposed doses of 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg, (b) (4) for once weekly or once monthly subcutaneous injection.

NDA 210136 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in

CAM2038, buprenorphine, is available currently as oral tablets, buccal film and as an implant indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS, the Probuphine REMS, and the Sublocade REMS.

As an injectable depot device, the CAM2038 formulation differs significantly from the sublingual and oral formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children, as well as misuse, and abuse. There are two approved products that are designed to be administered by a healthcare provider (HCP). One of these is Probuphine, an implantable device, is comprised of implantable rods that contain buprenorphine and carries the risks of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of the rods as well as the risks of accidental overdose, misuse and abuse. The other, Sublocade is the most similar to CAM2038 in terms of risk as it is a depot formulation of buprenorphine designed to be administered by a HCP and required a REMS to mitigate the risk of serious harm or death that could result from IV self-administration. The REMS for Sublocade consists of elements to assure safe use (i.e., healthcare setting certification), implementation system and a timetable for submission for assessments.

The Agency is particularly concerned about the risk associated with this product, because it is an injectable form of buprenorphine and will be available in prefilled syringes with needles attached. It is ready to inject and also easier to inject than other formulations, and is in a final product configuration that is typically dispensed for outpatient use. If CAM2038 is injected IV, the doses range from 8 mg (b) (4) and the formulation does not contain naloxone. There is a potential for abuse and misuse with this product since, given the proposed indication, many patients prescribed this mediation will have a history of IV drug abuse. Fifty percent of subjects in the clinical studies reported history of IV drug use. Importantly, as IV is not the proposed route of administration, results of IV injection were not studied in the clinical program and serious harm or death may result. The Agency is concerned that potential adverse events (AEs) that may result from IV injection such as tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression. A REMS with ETASU is necessary to ensure the benefits outweigh the risks.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210136 relevant to this review:

- 03/16/2017: In Pre-NDA meeting comments, the Agency informed Braeburn that all buprenorphine-containing products had a REMS and that if they chose not to submit a REMS with their NDA, they would need to include a rationale.
- 05/8/2017: Braeburn submitted NDA 210136 with no proposed REMS. They included a rationale document explaining their reasoning which included that the product's design restricts administration to healthcare settings only. They also

added that this formulation, specifically designed to be administered by HCPs in healthcare settings, does not pose some of the risks seen with take-home formulations.

- 08/23/2017: Braeburn submitted an inquiry to the Agency regarding whether the Review team had reviewed their rationale for exemption of a REMS program.
- 08/28/2017: The Agency responded that the need for a REMS was still under internal discussion, however their proposed restricted distribution to healthcare facilities such as physician offices and/or narcotic treatment programs (NTPs), did not include a description of how the restriction would be ensured. A teleconference to further discuss this matter was suggested.
- 09/5/2017: DRISK held a teleconference with Braeburn to discuss their proposed limited-distribution proposal and how this would be assured. The Agency generally agreed with the proposed distribution scheme, but stated that without a REMS, assuring that the product stayed within this scheme would be difficult.
- 11/1/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 210136. The committee discussed the sufficiency of the safety data and voted on if there was enough safety data to support all the proposed doses, some of the proposed doses or none of the proposed doses. The vote was 1:17:2 respectively, with most of the panel members stating that there is not enough data to support the higher doses. They were also asked to vote on the efficacy data to support either all, some or none of the doses. The vote was similar, 2:17:1, with most panelists agreeing that efficacy for the higher doses was not sufficient. The vote for approval of all, some or none of the proposed doses was 0:17:3. Many panelists agreed that six out of eight of the proposed doses (the lower six) should be approved. They were overwhelmingly in favor of restricted distribution and not allowing CAM2038 to be dispensed directly to patients. Some committee members expressed concern about access to the product in rural areas.
- 11/10/2017: Braeburn submitted a REMS submission amendment to their NDA. This consisted of a REMS Document only. The proposed goal was to mitigate the risks of misuse, abuse, accidental pediatric exposure and overdose while also providing sufficient access for appropriate patients, and inform prescribers, pharmacists and patients that CAM2038 should be administered only by a healthcare provider.

  The REMS Document included an ETASU to limit distribution of CAM2038 and proposed the following materials:
  - REMS Document
  - Supporting Document
  - Medication Guide
  - Healthcare Setting and Pharmacy Enrollment Form
  - Letters to Pharmacists and Providers
  - Training slide deck
  - Website
- 12/5/2017: The Agency held a teleconference with Braeburn that communicated that their program would need to include certification of all dispensing sites of

CAM2038. After the meeting, the Agency provided a draft templated Healthcare Setting and Pharmacy Enrollment Form for the Applicant to use as a guide to develop their own form. We also informed them that the materials listed below are necessary for their program and we planned to provide feedback, guidance and/or templates. The materials included:

  - REMS Document
  - Supporting Document
  - Healthcare Setting and Pharmacy Enrollment Form
  - Letters to HCP
  - Fact Sheet on How to Obtain CAM2038
  - Website Guidance Sheet

- 12/6/2017: The Agency emailed the draft materials described above to the Applicant.
- 12/13/2017: The Applicant submitted materials in response to the 12/5/2017 teleconference and 12/6/2017 emailed materials. These were submitted to the electronic document room (EDR), see below, and are the subject of this review.

2 MATERIALS REVIEWED

Braeburn Pharmaceuticals, Inc. REMS Amendment to NDA 210136 for CAM2038, submitted December 13, 2017 (Seq. No. 0066)

3 SUMMARY OF APPLICANT'S REMS SUBMISSION AND DRISK COMMENTS

3.1 ELEMENTS TO ASSURE SAFE USE

3.1.1 REMS DOCUMENT

In October of 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry[1] which provides updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug products. Because this is a new guidance, DRISK provided a draft REMS Document populated with the proposed CAM2038 REMS for their review on 12/6/2017. Braeburn reviewed the REMS Document and made a edits. One of the edits was to change the goal from including the word "self-administration" to "administration." Their proposed goal was:

The goal of the Tradename REMS is to mitigate the risk of serious harm or death that could result from intravenous administration by:

- Ensuring healthcare settings and pharmacies are enrolled and only dispense TRADENAME directly to a healthcare provider for administration by a healthcare provider

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

In addition, they proposed to change the word [redacted] to "enroll" in several places in the document. [redacted]

Reviewer Comment

Braeburn's proposal [redacted] *is not acceptable.* [redacted]

In terms of the change from [redacted] *to "enroll," we will inform Braeburn that changes to templated language in the REMS Document will require a justification. In general, Braeburn is in agreement with the REMS requirement* [redacted]

3.1.2 REMS SUPPORTING DOCUMENT

The Supporting Document describes Braeburn's proposed distribution plan and proposed operations. It also incorporates language from the proposed label and REMS Document.

Reviewer Comment

In the Supporting Document, Braeburn should provide additional details that clarifies the steps and processes for the distribution scheme and implementation of their proposed REMS program. For example, they need to describe which databases will be used by distributors to check that settings are enrolled in the program. Also, Braeburn needs to describe what type of pharmacies a HCP will use to order the product for named-patients, these details are missing. Therefore, Braeburn will need to provide further details on their proposed operations. In addition, Braeburn will need to align the Supporting Document with the current labeling and the REMS Document as they are being updated during the review of the application.

3.1.3 CAM2038 REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM

The Applicant received a templated draft Healthcare Setting and Pharmacy Enrollment Form on 12/6/2017. They made minimal changes to this form, except for one notable edit. Braeburn proposes that one authorized representative for a larger healthcare system, e.g. Kaiser, can enroll all healthcare settings that will order and dispense within the system and not submit the "Healthcare Setting and Pharmacy Information" section for each site.

Reviewer Comment

Braeburn will need to ensure accountability of each healthcare setting that orders and dispenses within a larger Healthcare system. We agree that one authorized representative can enroll several sites. However, the "Healthcare Setting and Pharmacy Information" section of the enrollment form will need to be submitted for each site.

3.1.4 CAM2038 REMS PROGRAM FACT SHEET

At the 12/5/2017 teleconference, DRISK informed the Sponsor that the Fact Sheet should describe how various stakeholders, such as DATA 2000 waivered providers, can obtain CAM2038. The Applicant submitted their proposed *CAM2038 REMS Program Fact Sheet* with minimal edits.

Reviewer Comment

See redlined version of this material for additional comments and edits.

3.1.5 DEAR HEALTHCARE PROVIDER LETTERS

On 12/6/2017, DRISK provided templated letters to Braeburn and the proposed letters were submitted with minimal edits.

Reviewer Comment

See redlined version of this material for additional comments and edits.

3.1.6 CAM2038 PROGRAM WEBSITE

On 12/6/2017, DRISK provided REMS website content guidance to Braeburn and the proposed REMS website screenshots were submitted with minimal edits.

Reviewer Comment

See redlined version of this material. The Applicant will need to include links to the Prescribing Information, Medication Guide, and all REMS materials on the website's navigation bar.

4 DISCUSSION AND CONCLUSIONS

DRISK determined that a REMS with ETASU is necessary to ensure the benefits of CAM2038 outweigh its risk of serious harm or death that could result from intravenous (IV) self-administration. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense CAM2038 to ensure that it is administered by healthcare providers and not dispensed directly to patients.

Overall, DRISK agrees with some of the minor changes made to several of the materials submitted by Braeburn on December 13, 2017 in their amendment to the NDA. However, they will need to maintain language that the goal of the REMS is to mitigate serious harm or death from intravenous self-administration and that the sites that dispense CAM2038 will be certified. They can address this and other edits provided in redlined versions with their next FDA submission.

5 COMMENTS FOR THE SPONSOR

The Agency has reviewed the Tradename REMS materials submitted on December 13, 2017 and has made new track changes and comments to the clean versions of the REMS materials and additional track changes and comments to the track change versions of the REMS Document and REMS Supporting Document. Specific comments regarding each REMS material is noted below:

Tradename REMS Document

Enrollment is the process to obtain certification; certification of healthcare settings is the REMS requirement, fulfills the ETASU and should be emphasized throughout the REMS Document and materials. Other changes to the REMS Document were minor and unless there is justification to change the templated language, the REMS Document language should remain the same as in the REMS Document we sent on December 6th. Although we are sending you the proposed REMS Document you submitted December 13th., please refer to the version the Agency provided on December 6th for any further edits or comments in your next submission.

Tradename REMS Supporting Document

Refer to our comments and edits. You need to clarify and provide further details on your operations. Please accept tracked changes before sending us the next version.

Tradename REMS Program Healthcare System Enrollment Form
Tradename REMS Program Fact Sheet: How to Obtain Tradename
Tradename REMS Program Letter for Healthcare Settings and Pharmacies

The Agency has accepted almost all the track changes proposed by you in the following materials. Please see the attached clean version (you submitted on Dec 13th) for additional revisions and comments from the Agency.

Tradename REMS Program Website Home Page Content:

The Agency has accepted almost all track changes. See the clean version for additional revisions and comments from the Agency. As noted previously, include links to the Prescribing Information, Medication Guide, and all REMS materials on the website's navigation bar. Add footer language as needed. Prior to approval of this REMS, the website screenshots must be submitted for the Agency's review - showing all content and functionality of the website, including the online enrollment process, footers, links, and the navigation bar.

General Comments:

- Continue to ensure that all content is consistent across all of the REMS materials and website.
- Continue to align all REMS materials with the REMS Document and the Prescribing Information, including the boxed warning, indication, and storage requirements language.
- As stated, while enrollment is the process to obtain certification, certification of healthcare settings should be emphasized. Therefore, retain all instances of

"certification" in all of the REMS materials - as noted in the version of REMS materials sent to you on December 6, 2017. Change this language throughout all of the REMS materials, REMS Document, and REMS Supporting Document back to what was originally proposed in the Agency's December 6, 2017 communication to you. This term aligns with the REMS Document and the similar REMS programs (e.g., Sublocade, Probuphine). Retain all other uses of "enroll" or "enrollment."

- Reinsert the term "self" in the term "intravenous self-administration" throughout all of the REMS materials, as this aligns with the REMS Document and REMS goal.

Resubmission Instructions:

Accept all changes with which you agree and submit tracked changed versions of the materials showing new proposed changes by Braeburn. The next submission to the Gateway should include Clean MS Word and Tracked MS Word of the following six documents:

- ***Tradename REMS Document***
- ***Tradename REMS Supporting Document***
- ***Tradename REMS Program Healthcare Setting and Pharmacy Enrollment Form***:
- ***Tradename REMS Program Letter for Healthcare Settings and Pharmacies***
- ***Tradename REMS Program Fact Sheet: How to Obtain Tradename***
- ***Tradename REMS Program Website Home Page Content***

ATTACHMENTS

1. TRADENAME REMS Document
2. TRADENAME REMS Supporting Document (email only)
3. TRADENAME REMS Program Healthcare Setting and Pharmacy Enrollment Form
4. TRADENAME REMS Program Dear Healthcare Provider Letter
5. TRADENAME REMS Program Fact Sheet: How to Obtain TRADENAME
6. TRADENAME REMS Website Content

16 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOMYA V DUNN
01/09/2018

CYNTHIA L LACIVITA
01/09/2018
Concur