CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

OTHER ACTION LETTERS

NDA 210136

COMPLETE RESPONSE

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

Attention: Susan Franks, MS
Senior Vice President of Regulatory Affairs

Dear Ms. Franks:

Please refer to your new drug application (NDA) dated and received July 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for BRIXADI (buprenorphine) extended-release injection for subcutaneous use.

We acknowledge receipt of your amendment dated June 15, 2021, which constituted a complete response to our December 1, 2020, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection for this application of the Pharmaceutics International (b) (4) (FEI 3006503102) manufacturing and testing facility located in Cockeysville, MD, and the Pharmaceutics International (b) (4) (FEI 1000513101) warehouse and testing facility located in Hunt Valley, MD, our field investigator conveyed deficiencies to the representatives of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated December 15, 2021.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition,

submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

PROPRIETARY NAME

Please refer to correspondence dated September 7, 2021, which addresses the proposed proprietary name, BRIXADI. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge the submission of your proposed modified REMS on July 6, 2021, which contains a Medication Guide, elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. We have no further comments on the BRIXADI REMS Document and REMS materials submitted on July 6, 2021; and the REMS Supporting Document and REMS Assessment Plan submitted on October 22, 2021, and amended December 1, 2021. We will make a final decision on your proposed modified REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our letter dated December 1, 2020, we have determined that, if this application is approved, you will be required to conduct postmarketing studies of BRIXADI to assess a known serious risk of precipitated withdrawal in patients whose initial injection of BRIXADI at a dose providing effective blockade of exogenous opioids (24 mg to 32 mg weekly; 64 mg to 96 mg monthly); and the unexpected risk of serious systemic histopathological changes, reproductive and developmental effects or cancer due to elemental impurities or leachables from the container closure into the drug product.

Specifically, we have determined that, if NDA 210136 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. Postmarketing clinical trial exploring how BRIXADI can be safely initiated at doses of 24 mg to 32 mg BRIXADI (weekly) without titration. The goals of the trial are to determine an accelerated dose-initiation regimen using BRIXADI (weekly) and assess the associated risks of precipitated withdrawal or inadequate dosing. Prespecify case definitions of precipitated withdrawal/lack of tolerability and dose inadequacy for the purposes of quantifying the risks of a more rapid initiation of BRIXADI (weekly).

2. Postmarketing clinical trial exploring how BRIXADI can be safely initiated at doses of 64 mg to 96 mg BRIXADI (monthly) without transferring from a period of treatment with another buprenorphine product. The goals of the trial are to determine an accelerated dose-initiation regimen using BRIXADI (monthly) and assess the associated risks of precipitated withdrawal or inadequate dosing. Prespecify case definitions of precipitated withdrawal/lack of tolerability and dose inadequacy for the purposes of quantifying the risks of a more rapid initiation of BRIXADI (monthly).

3. Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

4. Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

ADDITIONAL COMMENTS

We have the following comment that is not an approvability issue:

> Regarding your question about the adequacy of your elemental impurity evaluation, we do not agree you have provided adequate information to evaluate impurity levels in your drug product. As communicated to you in a recent information request dated August 27, 2021, we do not agree that (b) (4) (b) (4) used in report Ref. S52 REP S279_01 are the appropriate solvents for elemental impurities extraction. We refer you to USP <233> for possible concentrated acids to use as extraction solvents. The recommendation to evaluate elemental impurities, as noted in the tentative approval letter dated December 21, 2018, may be submitted as a post-marketing requirement.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Rita Joshi, Regulatory Project Manager, at rita.joshi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Celia Winchell, MD
Associate Director for Addiction Medicine
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

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/

CELIA J WINCHELL
12/15/2021 01:13:25 PM

NDA 210136

COMPLETE RESPONSE

Braeburn Inc.
450 Plymouth Road, Suite 400
Plymouth Meeting, PA 19462-1644

Attention: Susan Franks, MS
Senior Vice President, Head of Regulatory Affairs

Dear Ms. Franks:

Please refer to your new drug application (NDA) dated July 19, 2017, received July 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRIXADI (buprenorphine) extended-release injection for subcutaneous use.

We acknowledge receipt of your amendment dated June 1, 2020, which constituted a response to our December 21, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection for this application of the Pharmaceutics International (b) (4) (FEI 3006503102) manufacturing and testing facility located in Cockeysville, MD and the Pharmaceutics International (b) (4) (FEI 1000513101) warehouse and testing facility located in Hunt Valley, MD, our field investigator conveyed deficiencies to the representatives of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[3]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

Please refer to correspondence dated, August 16, 2018, which addresses the proposed proprietary name, BRIXADI. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge the submission of your proposed modified REMS on June 1, 2020, which contains a Medication Guide, elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. We will continue

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

discussion of your proposed modified REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our letter dated December 21, 2018, we have determined that, if this application is approved, you will be required to conduct postmarketing studies of BRIXADI to assess a known serious risk of precipitated withdrawal in patients whose initial injection of BRIXADI at a dose providing effective blockade of exogenous opioids (24 mg to 32 mg weekly; 64 mg to 96 mg monthly); and the unexpected risk of serious systemic histopathological changes, reproductive and developmental effects or cancer due to elemental impurities or leachables from the container closure into the drug product.

Specifically, we have determined that, if NDA 210136 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. Postmarketing clinical trial exploring how BRIXADI can be safely initiated at doses of 24 mg to 32 mg BRIXADI (weekly) without titration. The goals of the trial are to determine an accelerated dose-initiation regimen using BRIXADI (weekly) and assess the associated risks of precipitated withdrawal or inadequate dosing. Prespecify case definitions of precipitated withdrawal/lack of tolerability and dose inadequacy for the purposes of quantifying the risks of a more rapid initiation of BRIXADI (weekly).

2. Postmarketing clinical trial exploring how BRIXADI can be safely initiated at doses of 64 mg to 96 mg BRIXADI (monthly) without transferring from a period of treatment with another buprenorphine product. The goals of the trial are to determine an accelerated dose-initiation regimen using BRIXADI (monthly) and assess the associated risks of precipitated withdrawal or inadequate dosing. Prespecify case definitions of precipitated withdrawal/lack of tolerability and dose inadequacy for the purposes of quantifying the risks of a more rapid initiation of BRIXADI (monthly).

3. Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

4. Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the

course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Your assessment to establish a mode of action (MOA) for the NMP-induced tumorigenesis observed in the 18-month study in B6C3F1 mice did not include adequate information to clearly demonstrate that the findings are not human-relevant. The information submitted was inadequate to conclude that the NMP-induced effects are potentially attributed entirely to a Peroxisome Proliferator-Activated Receptor (PPAR) alpha-mediated mechanism as proposed. However, because a no-observed effect level (NOEL) was established in the mouse study that provided an 8-fold safety margin, we acknowledge that the risk to humans may not be significant. Therefore, no additional data are required, but the findings must be included in labeling. If you want to remove the language from labeling, you must submit a revised MOA assessment with additional data to bolster the weight of evidence that the tumorigenesis is driven by a PPAR alpha-mediated pathway. Refer to Klaunig et al., PPAR alpha Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance. Critical Reviews In toxicology 33(6): 655-780. 2003.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Matthew Sullivan, Chief, Project Management Staff, at (301) 796-1245, or via email at matthew.sullivan@fda.gov.

Sincerely,

{See appended electronic signature page}

Celia Winchell, MD
Associate Director for Addiction Medicine
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE:

- Labeling

51 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CELIA J WINCHELL
12/01/2020 04:15:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210136

TENTATIVE APPROVAL

Braeburn Pharmaceuticals Inc.
47 Hulfish Street
Suite 441
Princeton, NJ 08542

Attention: Susan Franks, PhD
Senior Vice President, Head of Regulatory Affairs

Dear Dr. Franks:

Please refer to your New Drug Application (NDA) dated and received July 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for BRIXADI (buprenorphine) extended-release injection for subcutaneous use, 8 mg, 16 mg, 24 mg, 32 mg, (weekly); 64 mg, 96 mg, and 128 mg (monthly).

We acknowledge receipt of your amendment dated June 26, 2018, which constituted a complete response to our January 19, 2018, action letter.

This NDA provides for the use of BRIXADI (buprenorphine) extended-release injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine product or who are already being treated with buprenorphine.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information, Medication Guide, and carton and container labeling). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the exclusivity protection or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the

legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Identify an unexpected risk of serious systemic histopathological changes, teratogenicity, serious embryo-fetal developmental, and/or post-natal developmental adverse events, or cancer due to exposure to NMP or the leachables from the container closure system including elemental impurities or currently unidentified compounds.

Furthermore, the new pharmacovigilance system that FDA is required to establish under Section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that if your application is approved, you will be required to participate in the conduct of the following postmarketing studies:

- Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data to characterize the elemental impurities that could be leached from the container closure system using suitable solvents (e.g., nitric acid for elementals from glass).

- Conduct a study to confirm, using validated methods, the identity of the unspecified (b) (4) the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) min, and the unknown compound with (b) (4) with RRT of (b) (4) min that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4) (b) (4) Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

- Conduct a fertility and early embryonic development study in female rats testing NMP administered via the subcutaneous route.

- Conduct a pre- and post-natal development study in rats testing NMP administered via the subcutaneous route.

Additionally, the controlled clinical trial was conducted in patients who initiated treatment with a test dose of sublingual buprenorphine/naloxone (SL BPN), followed by an injection of Brixadi (weekly) 16 mg. Patients then returned for up to two additional doses of Brixadi (weekly) 8 mg during the ensuing week. In the current medical climate, there is great interest in initiating treatment using a depot formulation as rapidly as possible, increasing the likelihood of the patient adherence to treatment from the outset and ensuring blockade effects are obtained as quickly as possible. It is, therefore, anticipated that clinicians may elect to accelerate the initiation of BRIXADI treatment by omitting the titration over the first week. However, because the doses of buprenorphine provided by BRIXADI at doses providing effective blockade of exogenous opioids are higher than doses of SL BPN typically used to initiate treatment, there is a risk that precipitated withdrawal, a clinically serious condition, could occur if BRIXADI is initiated without a period of titration. Further information on how BRIXADI could be initiated without titration would contribute to safer use of the drug.

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the following known serious risks:

- Evaluate precipitated withdrawal in patients whose initial injection of BRIXADI is at a dose providing effective blockade of exogenous opioids (24 mg to 32 mg weekly).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

- Conduct a postmarketing clinical trial exploring how BRIXADI can be safely initiated at doses of 24 mg to 32 mg BRIXADI (weekly) without titration. The goals of the trial are to determine a tolerable dose-initiation regimen using BRIXADI and assess the associated risk of precipitated withdrawal. Prespecify the case definition of precipitated withdrawal/lack of tolerability for the purposes of quantifying the risks of a more rapid initiation of BRIXADI.

Additionally, while not an approvability issue, we have the following comment:

> Your assessment to establish a mode of action for the NMP-induced tumorigenesis observed in the 18-month study in B6C3F1 mice did not include adequate information to clearly demonstrate that the findings are not human relevant. The information submitted was inadequate to conclude that the NMP-induced effects are potentially attributed entirely to a PPAR alpha-mediated mechanism as proposed. However, because a NOEL was established in the mouse study that provided an 8-fold safety margin, we acknowledge that the risk to humans may not be significant. Therefore, no additional data are required, but the findings must be included in labeling. If you want to remove the language from labeling, you must submit a revised MOA assessment with additional data to bolster the weight of evidence that the tumorigenesis is driven by a PPAR alpha-mediated pathway. Refer to Klaunig et al., PPAR alpha Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance. Critical Reviews In toxicology 33(6): 655-780. 2003.

If this application is ultimately approved, submit the protocols to your IND 114082, with a cross reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)
REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)
REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)].

As noted in our Complete Response letter dated January 19, 2018, in accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for BRIXADI to ensure the benefits of the drug outweigh the risk of serious harm or death that could result with intravenous self-administration.

Your proposed REMS, submitted on December 17, 2018, amended and appended to this letter, can be approved with your application. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

If your application is ultimately approved, your REMS must be fully operational before you introduce BRIXADI into interstate commerce. Furthermore, our letter of approval will provide the details of the assessment plan for BRIXADI.

If you have any questions, call Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling
- REMS

126 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON H HERTZ
12/21/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210136

COMPLETE RESPONSE

Braeburn Pharmaceuticals Inc.
47 Hulfish Street
Suite 441
Princeton, NJ 08542

Attention: Sheila Mathias, PhD
Senior Director, Regulatory Affairs

Dear Dr. Mathias:

Please refer to your New Drug Application (NDA) dated and received July 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for BRIXADI (buprenorphine extended-release) injection for subcutaneous use, 8 mg, 16 mg, 24 mg, 32 mg weekly; 64 mg, 96 mg, 128 mg (b) (4) monthly.

We also acknowledge receipt of your amendments dated December 14, 21 and 22 (2), 2017, and January 4, 5, 9 (2), and 12, 2018, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

1. There are insufficient clinical data (b) (4)

   Information needed to resolve deficiency
   Provide additional data (b) (4) or withdraw it from the application.

2. The submitted clinical datasets were found to include a number of discrepancies and errors, which you have determined were likely caused by limited QC/edit function checks between the IVR database and the clinical database.

Information needed to resolve deficiency
We acknowledge that you have resubmitted datasets which are intended to correct these errors. The resubmitted data were not reviewed for this action.

In addition to the datasets, submit a document describing the nature of the errors. Provide documentation of any auditing procedures performed to ensure that the datasets are reliable and that all errors have been identified and addressed.

Further, there are incomplete responses to prior information requests. For example, the response to the November 16, 2017, information request (IR) about Subject HS-11-421-(b) (6) who appeared to have two doses of study drug on the first day of treatment, noted that the subject received the SL BPN test doses and one dose of the 16 mg weekly formulation. However, there was no explanation as to why the kits were administered at the exact same time or whether any time elapsed from the test dose to the study dose. Similarly, you noted that Subject HS-11-421-(b) (6) did not receive a 32 mg dose on Day 3 of the study, as the subject was in the SL BPN group. However, you did not provide an explanation as to how that error occurred or what measures were taken to ensure that the other data fields are accurate. Additionally, there were several subjects identified as having distinct visits on the same day. Of these subjects, you reported HS-11-421-(b) (6) as a lab error and HS-11-421-(b) (6) as an oversight during data.

For each of the data errors identified in prior information requests, and for any further errors identified in the corrected datasets, provide an explanation with relevant documentation as to how these errors occurred and were corrected.

3. The Summary of Clinical Safety and the Clinical Study Report for Study HS-11-421 did not include an evaluation of dose-response for either efficacy or safety, nor an analysis of whether any dose-related risks were balanced by incremental increases in efficacy. Responses to our information requests during the review cycle were limited to tabulations without comments or conclusions.

   Information needed to resolve deficiency
   Provide a revised Summary of Clinical Safety and Summary of Clinical Efficacy that includes analysis and discussion of the dose-response relationships and how they inform the overall balance of risk and benefit.

4. The adverse event datasets (HS-11-421) lacked some relevant data fields. A response to an information request resolved only some of the issues. The dataset lacked variables necessary to identify patterns between adverse events and actions taken (e.g., dose increased and drug interrupted) and the dose a patient was taking when the adverse event occurred. Additionally, 35 entries of adverse events were not listed by dose or formulation in the dataset.

   Information needed to resolve deficiency
   We acknowledge that you have resubmitted datasets which are intended to correct discrepancies in the datasets and the resubmitted data will be reviewed in the next review

cycle. However, for the safety datasets (i.e., ADSL and ADAE) specifically, ensure that the following variables are included: ORALDAY; ORALDOSE; INJECTIONDAY; INJECTIONDOSE; INJECTION FORM; LASTFULL EXPOSURE. Create a flag that indicates if a patient received a supplemental dose of CAM2038. Note that, as discrepancies or missing data are identified in the patient populations, narratives describing the nature of these findings should be generated and submitted.

5. Regarding financial disclosures, descriptions of the steps taken to minimize bias were not provided for the clinical investigators that received large honoraria.

   Information needed to resolve deficiency
   Provide descriptions of the steps taken to minimize bias of the site investigators who received any large honoraria for Studies HS-11-421, HS-13-478, and HS-14-499.

NONCLINICAL

6. You have not provided adequate extractables studies to fully characterize the potential leachables profile of the proposed container closure system. Specifically, the studies submitted with the NDA did not employ sufficiently exhaustive conditions (b) (4) [redacted] We acknowledge that your TTCs were based on concepts outlined in ICH M7, and this guidance notes that the acceptable daily intake for genotoxic impurities may be based on total number of dosing days over a lifetime. However, your product is intended to provide continuous exposure to the API for the duration of dosing. Due to the way in which the drug depot is intended to form in subcutaneous tissue after drug administration, leachables arising from the container closure system are likely to be incorporated into the depot (b) (4) [redacted] (b) (4) [redacted] Consequently, patients may be exposed to leachables over the same duration the API is released; at least 7 days and 28 days for the weekly and monthly formulations, respectively. Moreover, treatment for opioid abuse disorder may exceed 10 years. Therefore, your AETs must be able to detect any compound that could be exposed at 1.5 mcg/day or greater. We acknowledge that you have initiated new extractables studies to address these concerns. However, these new data were not provided in time for review for this action.

   Information needed to resolve deficiency
   Submit final study reports for extraction studies testing (b) (4) [redacted] (b) (4) [redacted] employing rigorous extraction techniques in accordance with ***USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*** and ensure that your analytical methods are capable of detecting any compound over 1.5 mcg/day. Use these data to inform which compounds are to be monitored in the leachables studies.

7. You have not provided an adequate leachables evaluation to justify the safety of the proposed container closure system. Specifically, your leachables evaluation did not evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies as advised at the March 16, 2017, Pre-NDA meeting, and in accordance with best practices per ***USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems***.

   Information needed to resolve deficiency
   Conduct a new leachables study that evaluates at least three batches of the to-be-marketed weekly and monthly drug products and include assessments at multiple timepoints over the course of stability studies (beginning, middle, and end of proposed shelf-life) in order to identify trends in leachable levels over time. In the materials tested, include any secondary container closure systems, if present, and subject these materials to the same sterilization methods, as appropriate. Use the results of the extraction studies to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. For all drug products, establish the AET to be able to detect any compound that could be present at 1.5 mcg/day or greater. If you cannot meet these thresholds, safety evaluations should be based on the limits of quantitation (LOQ). In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. Provide a toxicological risk assessment that qualifies any leachable detected at or greater than 1.5 mcg/day from a genotoxicity perspective and any leachable detected at or greater than 5 mcg/day from a general toxicity perspective. Include copies of all referenced studies upon which a safety assessment is based. We acknowledge that you initiated new leachables studies during this review cycle; however, these new data were not provided in time for review for this action. Submit final study reports for leachables studies that take into consideration the comments outlined above with your resubmission.

8. You have not provided adequate pharmacokinetic data to appropriately calculate exposure margins for buprenorphine in your labeling. Although you have provided $AUC_{0\text{-}24h}$ data in animals, you have only provided human AUC_{ss} data. The exposure margins based on AUC in the labeling are to be based on the worst-case exposures in humans over the treatment period at steady state.

   Information needed to resolve deficiency
   Provide mean partial AUC (24-hour interval) data in humans at steady state that represents the highest exposures over any given 24-hour period to inform labeling.

9. You have not provided adequate justification that the cited published data on the reproductive and developmental effects of NMP adequately address all standard toxicological endpoints for reproductive and developmental toxicity studies. Further, you have not provided adequate data to bridge the published and unpublished studies which

employed routes other than the proposed clinical route. Although the data suggest some degree of safety following the different routes of administration, lack of adequate toxicokinetic data and inclusion of all standard endpoints in these studies preclude definitive conclusions regarding the potential risk of NMP via your drug product on these endpoints.

Information needed to resolve deficiency
Conduct definitive reproductive and developmental studies with NMP administered via the SC route. Alternatively, provide adequate PK bridging studies to the existing studies and clearly delineate how the referenced studies address all standard endpoints for fertility and early embryonic development, embryofetal development in two species, and pre- and postnatal development. Draft unpublished study reports are not acceptable as they may not reflect the final presentation of the data. Should you elect to conduct bridging studies, your resubmission must also include a discussion regarding the impact of the safety margins for reported effects of NMP given the known risks to these endpoints from buprenorphine.

10. You have not provided an adequate scientific bridge to the referenced published studies testing diacylglycerol oil (DAG) as a surrogate chemical solution for glycerol dioleate (GDO) for the effects of this novel excipient on rat fertility and early embryonic development, rat embryofetal development, rodent general toxicity, or rat and mouse carcinogenicity.

    Information needed to resolve deficiency
    As discussed at the February 24, 2015, End-of-Phase 2 meeting, provide data to support your conclusion that the DAG oil tested in these publications contains GDO at levels which provide an adequate characterization of the effects of GDO on these required studies.

11. You have not provided a rabbit embryo-fetal development study for the new excipient GDO.

    Information needed to resolve deficiency
    Either conduct an EFD study in the rabbit testing GDO or provide adequate justification why a study is not necessary.

12. You have not provided adequate justification for your conclusion that there is no carcinogenic potential of NMP even though your toxicological risk assessment of NMP noted hepatic tumors in mice.

    Information needed to resolve deficiency
    Conduct a mode of action assessment for N-methyl-pyrrolidone-induced mouse hepatocellular adenomas and carcinomas to inform the human risk assessment for NMP.

PRODUCT QUALITY

Facilities (Office of Process and Facilities)

13. During a recent inspection of the Pharmaceutics International, Inc. (Pii), Hunt Valley (FEI: 1000513101) testing facility for this application, our field investigator conveyed deficiencies to the facility.

    Information needed to resolve deficiency
    Pharmaceutics International, Inc. (Pii) must resolve these issues before this application may be considered for approval.

14. It is unclear in your NDA submission if [redacted] (b) (4) is the only source for the final manufacturing of the drug substance, buprenorphine base.

    Information needed to resolve deficiency
    Provide a statement in section 3.2.S.2.1 that the only source for the final manufacturing of the drug substance is from [redacted] (b) (4) FEI [redacted] (b) (4) If additional manufacturing sites will be used, update section 3.2.S.2.1 and the FDA Form 356h accordingly.

15. In your December 14, 2017, FDA Form 356h, you indicate that [redacted] (b) (4) conducted container closure integrity testing, break-loose testing, and glide force testing during development. However, it is unclear who will conduct these tests for the commercial batches based on the review of Module 3 and your FDA Form 356h.

    Information needed to resolve deficiency
    Identify the facilities that will conduct the container closure integrity testing, the break-loose testing, and the glide force testing for your commercial stability program and update Module 3 and your FDA Form 356h accordingly.

CDRH

16. We acknowledge your October 19, 2017, response to clarify how each facility is responsible for the manufacturing or design activities that complies with 21 CFR 820 to meet the requirements of 21 CFR Part 4. Because [redacted] (b) (4) was responsible for the Design History File and Design Verification Activities during development, additional information is needed.

    Information needed to resolve deficiency
    a. Describe how [redacted] (b) (4) meets the requirement for CFR 820.20, management responsibility. Provide a summary of how the facility's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).

b. Describe how [redacted] meets the requirement for 21 CFR 820.30, design control. Explain how the facility utilized the design control process to develop the combination product under review and provide a description of the design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product. Explain how the facility utilized the design control process to develop the combination product under review.

c. Describe how [redacted] meets the requirement for 21 CFR 820.100, corrective and preventive actions. Summarize the procedure(s) for the facility's Corrective and Preventive Action (CAPA) System. The CAPA system should require:

   i. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products,

   ii. Investigation of nonconformities and their causes,

   iii. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities, and

   iv. Verification or validation of the actions taken.

17. You have inadequately addressed how Pharmaceutics International, Inc. (FEI 3006503102) and [redacted] (FEI [redacted]) meet the requirement for 21 CFR 820.50, purchasing controls. Your response listed the different procedures within the purchasing control system, but no description of how they operated, to demonstrate meeting the requirements of 21 CFR 820.50, was provided.

    Information needed to resolve deficiency
    Provide a comprehensive summary of the procedures for purchasing controls for each facility. The summary should include the following:

    a. Describe the facility's supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.

    b. Define how the facility maintains records of acceptable suppliers and how the facility addresses the purchasing data approval process.

    c. Explain how the facility will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

    d. Explain how the procedure(s) will ensure that changes made by

contractors/suppliers will not affect the final combination product. Provide a description of how the facility applies the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

18. You have inadequately addressed how Pharmaceutics International Inc. (FEI3006503102) and (b) (4) (FEI (b) (4)) meet the requirement for 21 CFR 820.100, corrective and preventive actions. Your response listed the different procedures within the CAPA system, but no description of how they operated or demonstrated to meet the requirements of 21 CFR 820.100 was provided.

    Information needed to resolve deficiency
    Provide a comprehensive summary of the procedure(s) for Corrective and Preventive Action (CAPA) System for each facility. The CAPA system should require:

    a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products,

    b. Investigation of nonconformities and their causes,

    c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities, and

    d. Verification or validation of the actions taken.

Microbiology

19. The information concerning container-closure integrity testing (CCIT) of post-approval stability samples provided in your submission dated December 8, 2017, is acknowledged. However, additional information is needed.

    Information needed to resolve deficiency
    a. In your December 8, 2017, submission, you indicated that the CCIT visual analysis procedure was optimized to reduce variability in the analysts' assessment (b) (4) (b) (4) Describe the changes made to the procedure and explain how these changes reduce variability in the (b) (4) assessment.

    b. Provide the results of the study testing the reproducibility of the limit of detection for each weekly and monthly drug product presentation.

    c. If acceptable reproducibility data cannot be obtained, revise the post-approval stability specification to replace the CCIT visual analysis method with an alternative quantitative CCIT method or with sterility testing. If an alternative CCIT method is proposed, provide method validation.

Drug Product

20. It is not clear [redacted] The application contains no analytical measurement to monitor changes in the performance of the excipients over the shelf-life of the product.

    Information needed to resolve deficiency

    a. As previously agreed, provide [redacted] a release and stability specification. Justify how this method will accurately demonstrate [redacted]

    b. Using HPLC, GC, or similar modern quantitative analytical method, provide release and stability data [redacted]

    c. Using HPLC, GC, or similar modern quantitative analytical method, provide release and stability data [redacted]

    d. Provide [redacted] testing on release and stability in the drug product.

21. It is not clear that dose delivered testing by weight is representative of the dose being delivered to the patient.

    Information needed to resolve deficiency
    Provide side-by-side testing utilizing delivered dose by HPLC and Uniformity of Dosage Units (UDU) by weight testing for the drug product process performance qualification (PPQ) batches at release. Compare the datasets and justify how the data by weight are representative of the dose delivered to the patient.

22. Module 3.2.P.2.4, Container Closure System, contains the statement "*It is critical that the CAM2038 q1w drug product contains the target ethanol content of 10% w/w at release.*" However, the ethanol content specification for the 8 mg and 16 mg weekly presentations is [redacted]% w/w, which is excessively wide.

    Information needed to resolve deficiency
    Tighten the ethanol content specification for the 8 mg and 16 mg weekly presentations.

23. The level of precision in the glycerol dioleate specification is [redacted] (b) (4)

    Information needed to resolve deficiency
    Provide a specification in which the glycerol dioleate specification [redacted] (b) (4) Refer to the USP40-NF35 monograph.

24. Data were not provided on the effect of storage orientation on the drug product shelf-life.

    Information needed to resolve deficiency
    Provide stability data on the upright and inverted storage orientations.

25. No freeze/thaw data were provided for the drug product.

    Information needed to resolve deficiency
    Provide the results of a freeze/thaw study by performing stability testing on samples stored at 0°C, as well as a cycling study including three cycles consisting of two days at 0°C and two days at 40°C (twelve days total).

26. Your application referenced the Drug Master File (DMF) [redacted] (b) (4), which was referenced for [redacted] (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on January 4, 2018.

    Information needed to resolve deficiency
    These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

PRESCRIBING INFORMATION

27. The following represent high-level comments regarding the proposed labeling:

    a. Any claims about the blockade effectiveness of BRIXADI should be limited to the weekly formulation, since no blockade data were provided for the monthly formulation.

    b. Some other claims and extrapolations for the monthly formulation, which were in fact observed only for the weekly formulation, may not be supported.

    c. Note the following comments about specific sections of labeling:

INDICATION AND USAGE

You proposed the following indication statement:
(b) (4)

Modify the language to clearly identify the different uses of the Weekly and Monthly Products, and to limit use to treating moderate to severe opioid use disorder.

DOSAGE AND ADMINISTRATION

Reorganize the proposed labeling to clearly identify the uses of the Weekly and Monthly Products and the approach to dose conversion. The starting dose should be revised from the proposed (b) (4) weekly at the first injection to the regimen studied in the clinical trials (16 mg weekly, followed by additional 8 mg weekly at subsequent visits later the same week).

The recommended injection sites should be limited to the abdomen, buttock, and thigh because the arm site did not yield BE results.

INSTRUCTIONS FOR USE

i. You state in the SELECTING AN INJECTION SITE section that *[Trade name]* (b) (4) *should not be administered to the same site of injection for at least 8 weeks* (b) (4) It is unclear if the monthly injection should never be administered to the same site of a previous injection or if a specific amount of time is needed to elapse. Additionally, it is unclear (b) (4) We note comprehension testing of the statement was not conducted during the HF validation study. We are concerned the statement may be misinterpreted resulting in wrong administration techniques errors. To mitigate wrong administration technique errors, we recommend you clarify if there is a specific amount of time that should elapse (e.g., "X" weeks) before administering the monthly injection to the same site of a previous injection. Additionally, clarify the intended meaning (b) (4)

ii. The highlighted area of the abdomen in Figure 5 under SELECTING AN INJECTION SITE appears (b) (4) We note Figure 5 was revised in the IFU used during the HF validation study, however, Figure 5 remained unchanged in the IFU included in the November 30, 2017 draft submission of the proposed intend-to-market IFU. We previously communicated during review of the HF validation study protocol that this highlighted area could be misinterpreted (b) (4)

[redacted] (b) (4)

To mitigate wrong administration technique errors, ensure the highlighted area [redacted] (b) (4)

WARNINGS AND PRECAUTIONS
Add language highlighting the difference between the formulations.

CLINICAL TRIALS EXPERIENCE
Separate the data to show dose-effects and formulation effects, and to list all events occurring at a 2% or more in the CAM arms.

28. We reserve further, more detailed comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

    If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

MEDICATION GUIDE

29. Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

PROPRIETARY NAME

30. Please refer to correspondence dated January 12, 2018, which addresses the proposed proprietary name, BRIXADI. This name was found conditionally acceptable pending approval of the application in a future review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)].

We acknowledge receipt of your proposed REMS on October 10, 2017, which contains a Medication Guide, elements to assure safe use (ETASU), an implementation system and a timetable for submission of assessments of the REMS.

In accordance with section 505-1 of the FDCA, we have determined 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.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Carton and container labeling

a. Reference is made to your draft labeling submission dated November 30, 2017. You are proposing to market professional samples for each weekly and monthly strength of buprenorphine extended-release injection. Submit container label and carton label mock-ups for each professional sample for Agency review.

b. Ensure the lot number and expiration date is included on the final syringe labels and cartons for each buprenorphine weekly and monthly injection per 21 CFR 201.10(i)(1) and 21 CFR 201.17. Additionally, we note the inclusion of an additional "Rx Only" statement shown above the NDC number on the buprenorphine 8 mg syringe label, which should be removed.

c. We note the unit of measurement (i.e. °C and °F) does not follow each numerical value of the temperature range within the storage statement on each carton. The acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality. To provide clarity, we recommend revising the temperature statement on each carton to read: Store at 20°C to 25°C (68°F to 77°F); with excursions permitted to 15°C to 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

d. We acknowledge the revision to the product code of each NDC; however, we note the NDC package code (last 2 digits) for the buprenorphine weekly and monthly strengths 16 mg/0.32 mL and higher does not correspond to the package size. Each carton contains one unit of use, as such, the NDC package code typically aligns with the package size. We recommend you consider revising the NDC number on each syringe label and carton so the package code reflects "01" as the package size (e.g. revise to 58284-016-01, 58284-064-01, etc.). Additionally, ensure the NDCs are updated in the prescribing information accordingly.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Taiye Ayoola, PharmD, Regulatory Project Manager, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SHARON H HERTZ
01/19/2018