

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

OTHER REVIEW(S)

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 020733, Suboxone sublingual tablets	FDA's previous finding of safety and effectiveness

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Pivotal relative BA/BE Study BNX-110: 4.2/0.696 mg BEMA buprenorphine NX film vs. 8/2 mg Suboxone SL tablet. This study was completed prior to when that product was discontinued from marketing.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
*If "NO," proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Suboxone sublingual tablets	020733	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO
If “YES”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO
If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing: Suboxone tablets

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO
(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a change in dosage form, from tablet to buccal film, as well as a change in the ratio of buprenorphine:naloxone.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Suboxone sublingual tablets, NDA 022733 (listed product)

Suboxone sublingual film, NDA 022410

Zubsolv sublingual tablets, NDA 204242

Additionally, ANDAs to Suboxone sublingual tablets are also approved.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

MATTHEW W SULLIVAN
06/12/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Office of Medication Error Prevention and Risk Management

CRC Packaging and Labelling Review

Date: June 5, 2014
From: Kellie Taylor, PharmD, MPH
Deputy Director, OMEPRM
To: Rigoberto Roca, MD
Deputy Director, DAAAP
Drug Name and Strength: Bunavail (buprenorphine/naloxone) buccal film
Application Type/Number: NDA 205637

1 INTRODUCTION

This review assesses whether the packaging employed for this drug product meets the Consumer Product Safety Commission's child-resistant packaging standards and provides recommendations for the labels and labelling accordingly.

2 MATERIALS REVIEWED AND FINDINGS

I reviewed the following materials:

- Test Report dated 12 May 2014 titled "Evaluation of the Fold over Tear or Use Scissors, (b)(4) Pouches for Child-resistant effectiveness for BioDelivery Sciences International."
- Carton labels, container labelling, prescribing information, and Medication Guide for NDA 205637

3 FINDINGS AND DISCUSSIONS

The methods described in the study reports for both the child-resistant testing and senior-use effectiveness are consistent with the test requirements for the Poison Prevention Packaging Act per CFR Title 16, part 1700.

For the child-resistant testing, the subjects included in the study are appropriate. The study employed 50 children (equal genders) aged 44-51 months as described in the PPA test protocol.,

and distribution of participants within the age bands for the pediatric subjects is appropriate and consistent with PPA regulations. Failure was defined by the investigators in the protocol as the ability to access 2 or more pouches (F=2 criteria). I disagree with the criteria for failure since as little as 1 or less than one unit of buprenorphine could be expected to produce serious injury or illness to a 25-pound child, which is the criteria ascribed in the PPA. In my view, the criteria for failure should have been the ability to access 1 or more pouches (F=1 criteria). Although I disagree with the pre-specified criteria for failure, in reviewing the data provide in Table 2 of the study report, I note that this is a moot point since no children accessed even one of the pouches. In other words, since the pouch prevent 100% of children tested from accessing the drug, the packaging meets the PPA standards for an F=1 child-resistant package.

For the senior-use effectiveness portion of the study, 100 seniors were employed with ages ranging between 50 to 70 years. The number of adult subjects is consistent with the PPA requirement. Seventy-percent of subjects ere female as described in the PPA regulations, and the adults were divided proportionally into three age groups (50-54, 55-59, and 60-70 years) as described in the PPA regulations. The senior-use effectiveness portion of the study reported 1 adult female (in the 55-59 age group) that could not open the package on the second demonstration. Therefore, the overall senior use effectiveness is 99%, which exceeds the PPA's standard of 90% effectiveness in the adult population tested.

4 CONCLUSION

Based on my review of the study report, I conclude that the foil pouch packaging proposed for NDA 205637 is child-resistant in accordance with the standards ascribed by the PPA. I also note that this packaging has met the PPA standards for senior-use effectiveness and therefore I do not expect it to hinder use by adults using this drug product.

I recommend that DAAAP allow the product to be labelled as child-resistant. However, I also recommend that language in the label and labelling thoughtfully advise on the safe storage of the drug product (i.e. in the package until time of use, and up and away from children) to avoid any potential implication that child-resistance is equated with "child-proof."

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/s/

KELLIE A TAYLOR
06/05/2014

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: June 5, 2014

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 205637

Product Name and Strength: Bunavail (Buprenorphine and Naloxone) buccal film
2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg

Product Type: Multi-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Biodelivery Sciences International, Inc. (BDSI)

Submission Date: June 4 and 5, 2014

OSE RCM #: 2013-2021

DMEPA Primary Reviewer: Vicky Borders-Hemphill, Pharm.D.

DMEPA Associate Director: Lubna Merchant, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the revised labels and labeling for Bunavail, NDA 205637, submitted by Bidelivery Sciences International Inc. (BDSI) in response to recommendations we provided in OSE review # 2013-2021 dated May 23, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the revised container labels and carton labeling submitted by BDSI on June 4 and 5, 2014 and determined that our previous recommendations were implemented. On May 30, 2014, the (b) (4) strength was withdrawn from the NDA and revised labels and labeling for this strength were not submitted for review.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling submitted June 4 and 5, 2014 are acceptable.

If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bunavail that Biodelivery Sciences International, Inc. submitted on April 29, 2014. The following product information is provided in the October 25, 2013 insert labeling submission.

Table 2. Relevant Product Information for Bunavail	
Active Ingredient	buprenorphine and naloxone
Indication	maintenance treatment of opioid dependence
Route of Administration	Buccal
Dosage Form	buccal film; each dosage unit is a yellow, rectangular film, with the mucoadhesive side of each film marked with a code (BN2, BN4, or BN6) corresponding to each unique strength.
Strength	2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg
Dose and Frequency	One buccal film daily The recommended target dosage is a single daily dose of (b) (4). The dosage should be progressively adjusted in increments/decrements of (b) (4) to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms. When two films are required for one dose, place one film on the inside of one cheek and the other film on the inside of the other cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time.
How Supplied and Container Closure	Each buccal film is individually wrapped in a protective foil package that is (b) (4) sealed and child resistant. There are 30 individually wrapped films per carton. The cartons will be (b) (4). The cartons will use the same identifying color coding as will be used for the various dosage strengths on the individual foil packages. The different strengths will be distinguished by color coding on the individual foil packages.
Storage	Store at 20 - 25°C (68 - 77°F), protected from freezing and moisture, until ready to use

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L drive on May 8, 2014 using the terms, Bunavail to identify reviews previously performed by DMEPA.

C.2 Results

OSE Review # and Date	Summary
# 2013-2021 March 7, 2014	We provided recommendations for the container label, carton labeling, and Medication Guide submitted August 7, 2013 and for the insert labeling October 25, 2013
# 2013-2021 May 23, 2014	We provided recommendations for the revised container label and carton labeling submitted April 29, 2014 and recommended the removal of the proposed single digit numerical descriptor found throughout labels and labeling

APPENDIX D. HUMAN FACTORS STUDY

N/A

APPENDIX E. ISMP NEWSLETTERS

N/A

APPENDIX F. Other

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Bunavail labels and labeling submitted by Biondelivery Sciences International, Inc. on June 4, 2014.

- Container (foil package) Labels
- Carton labeling

G.2 Label and Labeling Images

Container Labels

2.1 mg/0.3 mg film pouch submitted June 5, 2014



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRENDA V BORDERS-HEMPHILL
06/05/2014

LUBNA A MERCHANT
06/05/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 205637
Product Name: Bunavail (buprenorphine and naloxone)

PMR/PMC Description: A clinical trial to assess the risk of QT prolongation with Bunavail buccal film.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2015</u>
	Study/Trial Completion:	<u>06/30/2016</u>
	Final Report Submission:	<u>12/31/2016</u>
	Other: <u>Draft Protocol Submission</u>	<u>12/31/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Buprenorphine and naloxone is already approved and marketed for this indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

New safety information derived from clinical studies from the Butrans (buprenorphine transdermal system) development program for pain that revealed QT prolongation at the highest studied dose led to the PMR for a clinical trial to assess the risk of QT prolongation for Suboxone film for opioid dependence in 2010. This PMR for Suboxone film has not been completed, and thus the PMR is being required of other buprenorphine/naloxone products for opioid dependence indications as well.

We will also advise the sponsor not to utilize naltrexone blockade in any arm of the study as we have recently learned from another product in development that naltrexone may interfere with the effect of buprenorphine on cardiac repolarization.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial to assess the risk of QT prolongation. Naltrexone blockade should not be used because it may interfere with the effect of buprenorphine on cardiac repolarization.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Study that measures QT interval in patients, not in healthy volunteers

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

JUDITH A RACOOSIN
06/05/2014

LABEL AND LABELING REVIEW

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

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Date of This Review: May 23, 2014

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 205637

Product Name and Strength: Bunavail (Buprenorphine and Naloxone buccal film)
[REDACTED] ^{(b) (4)} 2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg

Product Type: Multi-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Biodelivery Sciences International, Inc. (BDSI)

Submission Date: April 29, 2014

OSE RCM #: 2013-2021

DMEPA Primary Reviewer: Vicky Borders-Hemphill, Pharm.D.

DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the revised labels and labeling for Bunavail, NDA 205637, submitted by Bidelivery Sciences International Inc. (BDSI) in response to recommendations we provided in OSE review # 2013-2021 dated March 7, 2014. Additionally, BDSI proposes the addition of a single numerical digit descriptor next to the proprietary name.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other (Sponsors written response dated 4/11/2014)	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the revised container labels and carton labeling submitted by BDSI on April 29, 2014 and determined that our previous recommendations were implemented. However, (b) (4)

We evaluated the revised labels and labeling and determined that the use of color differentiation on labels and labeling are sufficient to provide packaging differentiation

and minimize the risk for selection error when dispensing. Also, the statements of strength are sufficiently prominent on the labels and labeling to allow for recognition and proper dispensing of the correct strength by the pharmacist. We evaluated film samples and determined that the imprint in the mucoadhesive side of the buccal film combined with the differences in film size are sufficient to provide product differentiation when administering two different Bunavail strengths. (b) (4)

[Redacted]

[Redacted]

We note there are trailing zeros after the decimal point (i.e., 4.2/0.70) in the statements of strength, and we recommend they be removed from revised labels and labeling to mitigate the risk for misinterpretation.²

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved for clarity and to increase the readability and prominence of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

¹ Institute for Safe Medication Practices. Safety briefs: Label confusion with Stalevo. ISMP Med Saf Alert Acute Care. 2011;16(10): 2-3.

² ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2013 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

Based on this review, DMEPA recommends the following be implemented prior to approval of NDA 205637:

A. Comments to the Division

1. Prescribing Information: General Comments

- i. To mitigate the risk of misinterpretation of strength, we recommend revising the statements' of strength values out to the tenths decimal place (per concurrence with ONDQA via email dated May 7, 2014) with no trailing zeros, like the following:

4.2/0.7

- ii.  (b) (4)

B. Comments to the Applicant

1. Foil package Labels and Carton Labeling

- i. We determined that the use of color differentiation on labels and labeling are sufficient to provide packaging differentiation between the proposed strengths.
- ii. To mitigate the risk of misinterpretation of strength information, revise the statement of each strength's value out to the tenths decimal place with no trailing zeros like the following:

4.2/0.7

- iii. To highlight more important information, place the strength statement in the colored box
- iv. Decrease the prominence of the "Rx Only" statement and relocate it from the colored box to the customary position in the upper right corner of the principal display panel

- v.  (b) (4)



If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

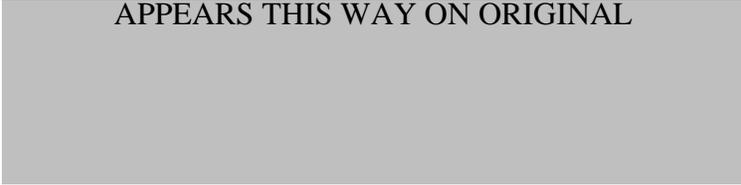
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bunavail that Biodelivery Sciences International, Inc. submitted on April 29, 2014. The following product information is provided in the October 25, 2013 insert labeling submission.

Table 2. Relevant Product Information for Bunavail	
Active Ingredient	buprenorphine and naloxone
Indication	maintenance treatment of opioid dependence
Route of Administration	Buccal
Dosage Form	buccal film; each dosage unit is a yellow, rectangular film, with the mucoadhesive side of each film marked with a code (BN2, BN4, or BN6) corresponding to each unique strength.
Strength	(b) (4) 2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg
Dose and Frequency	One buccal film daily The recommended target dosage is a single daily dose of (b) (4). The dosage should be progressively adjusted in increments/decrements of (b) (4) to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms. When two films are required for one dose, place one film on the inside of one cheek and the other film on the inside of the other cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time.
How Supplied and Container Closure	Each buccal film is individually wrapped in a protective foil package that is (b) (4) sealed and child resistant. There are 30 individually wrapped films per carton. The cartons will b (b) (4) The cartons will use the same identifying color coding as will be used for the various dosage strengths on the individual foil packages. The different strengths will be distinguished by color coding on the individual foil packages.
Storage	Store at 20 - 25°C (68 - 77°F), protected from freezing and moisture, until ready to use

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)
N/A

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APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

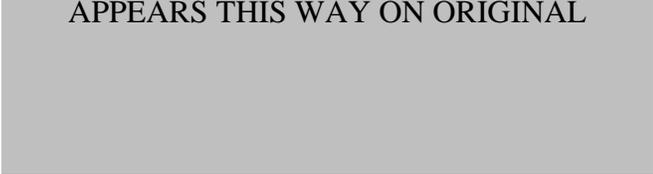
We searched the L drive on May 8, 2014 using the terms, Bunavail to identify reviews previously performed by DMEPA.

C.2 Results

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APPENDIX D. HUMAN FACTORS STUDY
N/A

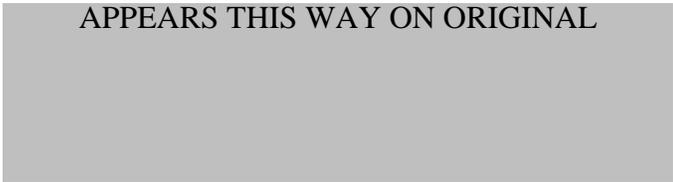
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APPENDIX E. ISMP NEWSLETTERS

N/A

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APPENDIX F. Sponsors written response dated 4/11/2014

(b) (4)



APPENDIX G. LABELS AND LABELING

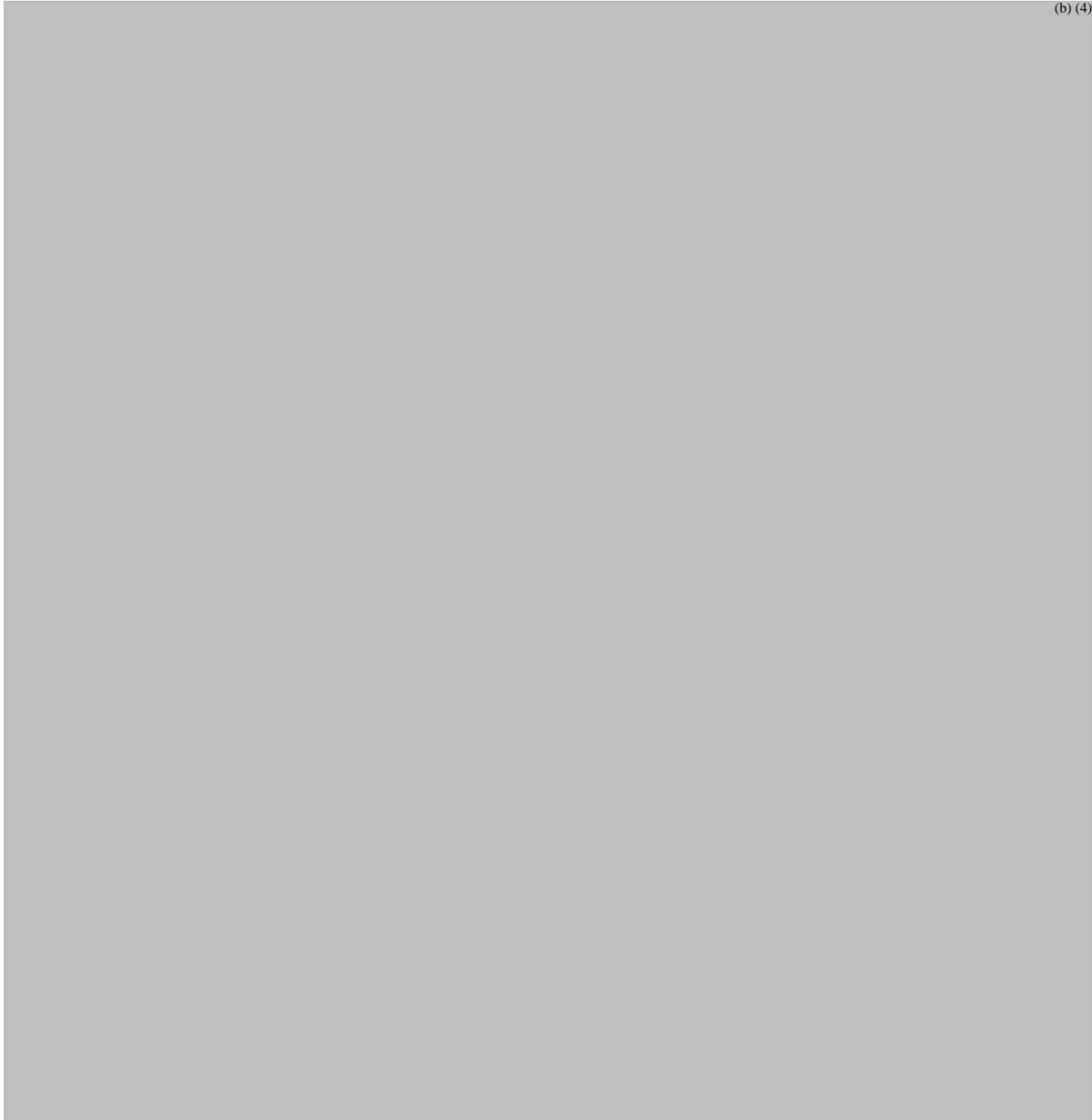
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Bunavail labels and labeling submitted by Biondore Sciences International, Inc. on April 29, 2014.

- Container (foil package) Labels
- Carton labeling

G.2 Label and Labeling Images

Container Labels



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BRENDA V BORDERS-HEMPHILL
05/23/2014

IRENE Z CHAN
05/23/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 23, 2014

To: Bob A. Rappaport
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BUNAVAIL (buprenorphine and naloxone)

Dosage Form and Route: buccal film, CIII

Application Type/Number: NDA 205-637

Applicant: BioDelivery Sciences International, Inc.

1 INTRODUCTION

On August 7, 2013, BioDelivery Sciences International, Inc. submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 205-637 for BUNAVAIL (buprenorphine and naloxone) buccal film. The reference listed drug is NDA 20733, SUBOXONE (buprenorphine and naloxone) sublingual tablets, held by Reckitt Benckiser Healthcare. The purpose of this submission is to seek approval for the proposed indication for the maintenance treatment of opioid dependence for BUNAVAIL (buprenorphine and naloxone) buccal film.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on September 4, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BUNAVAIL (buprenorphine and naloxone) buccal film.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft BUNAVAIL (buprenorphine and naloxone) buccal film MG received on August 7, 2013, and received by DMPP and OPDP on September 4, 2013.
- Draft BUNAVAIL (buprenorphine and naloxone) buccal film Prescribing Information (PI) received on August 7, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 8, 2014.
- Approved SUBOXONE (buprenorphine and naloxone) sublingual film comparator labeling dated April 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
05/23/2014

LATOYA S TOOMBS
05/23/2014

BARBARA A FULLER
05/23/2014

LASHAWN M GRIFFITHS
05/23/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: May 23, 2014

To: Matthew Sullivan, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 205637
OPDP labeling comments for BUNAVAIL (buprenorphine and naloxone)
buccal film, CIII
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for BUNAVAIL (buprenorphine and naloxone) buccal film, CIII (Bunavail) that was submitted for consult on September 4, 2013. Comments on the proposed PI are based on the version sent via email from Matthew Sullivan (RPM) on May 8, 2014 entitled "SCPI version for review.doc"

Comments regarding the PI are provided on the marked version below.

We have no comments on the draft carton/container labeling accessed from the following EDR location, \\cdsesub1\evsprod\NDA205637\0000

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
05/23/2014



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 13, 2014

To: Bob Rappaport, M.D., Director
 Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
 Controlled Substance Staff

From: Silvia N. Calderon, Ph.D., Team Leader
 Controlled Substance Staff

Subject: NDA 205637. Bunavail, Buprenorphine hydrochloride and naloxone hydrochloride, buccal films
Indication: Maintenance treatment of opioid dependence
Dosages: (b) (4) 2.1 mg/0.35 mg; 4.2 mg/0.7 mg and 6.3 mg/1.04 mg of buprenorphine hydrochloride and naloxone hydrochloride respectively.
Sponsor: BioDelivery Sciences International (BDSI)

Materials reviewed: NDA 205637 Proposed annotated draft labeling

Table of Contents

1 BACKGROUND1

2 CONCLUSIONS:2

3 RECOMMENDATIONS:.....3

1 Background

This memorandum responds to a consult request (dated September 3, 2013) from the Division of Anesthesia, Analgesia and Addiction Drug Products (DAAAP) to review NDA 205637 from the controlled substance perspective and to provide recommendations if deemed necessary.

Buprenorphine is a partial agonist at the mu-opioid receptor, and a Schedule III substance under the Controlled Substances Act (CSA). Naloxone is a mu opioid antagonist, which is supposed to be inactive when the product is used as indicated. However naloxone is intended to block the mu-opioid agonist effects of buprenorphine, if the film is manipulated for the purpose of parenteral or intranasal abuse. No abuse deterrent claims are being sought by the Sponsor.

Bunavail is a two layer polymeric film containing buprenorphine hydrochloride and naloxone hydrochloride. Buprenorphine is present in the mucoadhesive layer (ML), whereas naloxone is present in the backing layer (BL). The film is supposed to be used by placing the ML against the inside of the cheek, in such a way that the buprenorphine is absorbed through the buccal mucosa whereas the naloxone is swallowed.

The comparator drug product for this 505(b)(2) application is Suboxone tablets (NDA#20733), which contains buprenorphine and naloxone, and is no longer marketed. The film contains a higher ratio of buprenorphine per dosage unit than the comparator product. The buprenorphine base/naloxone base ratio is 6:1 in the films, and 4:1 in Suboxone tablets. The Sponsor conducted in vitro studies to demonstrate that naloxone is extracted in combination with buprenorphine when the film is manipulated, and that the amount of naloxone extracted would be sufficient to precipitate withdrawal if the extraction solution were injected. The Sponsor conducted the in vitro studies in accordance with the “FDA Draft Guidance – Abuse-Deterrent Opioids – Evaluation and Labeling.” However, the Sponsor is not seeking abuse deterrent claims.

In these studies the Sponsor compared the percentages of buprenorphine and naloxone extracted from the films to those extracted from Suboxone tablets, using several solvents. Extractions were conducted using techniques and solvents that may be readily available to a user. Extractions were carried out for a period of time until the film completely dissolved or the majority of the product was extracted. Extractions were conducted using (b) (4) of the selected solvents for the film samples and (b) (4) of solvent for the tablets. Selected solvents include (b) (4)

CSS did not conduct a primary review of the in vitro studies provided by the Sponsor. For the in vitro studies performed by the Sponsor, CSS relies on the findings in the CMC review. For full review of the “In Vitro Extraction Study of BEMA Buprenorphine-Naloxone (BNX) Buccal Soluble Films,” see DARRTS, NDA 205637, Shaw, Arthur B., review dated May 6, 2014.

The Sponsor submitted pharmacokinetic data to demonstrate that the 4.2 mg/0.7 mg strength of the film is bioequivalent to the 8 mg/2 mg tablet strength.

2 Conclusions:

1. As stated in the CMC review (DARRTS, NDA 205637, Shaw, Arthur B., review dated May 6, 2014), in vitro studies showed that among all solvents tested, buprenorphine is extracted selectively in (b) (4) from both products, leaving the naloxone behind. Temperature, and cutting or grinding have little effect on differential extraction. A distinctive feature of the film is that it does not dissolve in the (b) (4) solution, whereas the tablet forms a suspension in the (b) (4) solution. These data indicate that when compared to the tablets, the film is vulnerable to extraction, and could be sought by

abusers as a source of injectable buprenorphine. However, the tablets are no longer on the market and have been replaced by Suboxone films.

Bunavail was not compared to the currently available Suboxone films in in vitro extractability studies. The FDA laboratory in Saint Louis is in the process of conducting these extraction studies.

2. Naloxone was extracted preferentially in [REDACTED] (b) (4).
3. In vitro studies demonstrate that buprenorphine is extracted in combination with naloxone using [REDACTED] (b) (4).
4. Although buprenorphine can be selectively extracted from the naloxone present in the film using [REDACTED] (b) (4), the language proposed by the Sponsor under Section 5.8 – Precipitation of Opioid Withdrawal Signs and Symptoms- of the label, still applies. It is likely that the naloxone extracted from the film in combination with buprenorphine using common extraction solvents such as [REDACTED] (b) (4) will precipitate withdrawal signs and symptoms if the film were abused by the parenteral route by individuals dependent on full opioid agonist.

Section 5.8 – Precipitation of Opioid Withdrawal Signs and Symptoms currently reads:

Because it contains naloxone, BUNAVAIL buccal film is [REDACTED] (b) (4) likely to produce [REDACTED] (b) (4) withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine and methadone. Because of the partial agonist properties of buprenorphine, BUNAVAIL buccal film may precipitate withdrawal signs and symptoms in such persons if administered buccally before the agonist effects of the opioid have subsided.

5. Section 9- Drug Abuse and Dependence is identical to the one in the Suboxone (Tablets) label

3 Recommendations

No specific recommendation at this time.

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/s/

SILVIA N CALDERON
05/13/2014

MICHAEL KLEIN
05/13/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2014

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)
Office of Drug Evaluation II

FROM: Arindam Dasgupta, Ph.D.
Pharmacologist, BE Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Chase Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 205-637, Buprenorphine and
Naloxone buccal film, sponsored by BioDelivery
Sciences International

At the request of the Division of Anesthesia, Analgesia, And
Addiction (DAAAP), the Division of Bioequivalence and GLP
Compliance (DBGLPC) audited the clinical analytical portions of
the following bioequivalence study:

Study #1: BNX-110
Study Title: "A Comparison of the Rate and Extent of
Buprenorphine Absorption from BEMA
Buprenorphine NX Films and Suboxone Tablets and
Films"

The clinical portion of the study was audited at Worldwide Clinical Trials Early Phase Services LLC, San Antonio, TX by ORA Investigator Joel Martinez between December 4 and December 9, 2013. The analytical portion of the study was audited at

(b)(4) by (b)(4)

(OSI) between (b)(4). The audits included a thorough examination of facilities and equipment; examination of study records, including communications between sponsor and laboratory staff; and interviews and discussions with (b)(4) management and staff. Following the inspection of the analytical site, no objectionable conditions were observed and no Form FDA 483 was issued. Following the inspection of the clinical site, FDA 483 was issued. Response to FDA 483 dated January 14, 2014 was received by OSI on April 23, 2014.

The 483 observation for study BNX-110 (clinical), WCT's response, and our evaluations follow:

Clinical Site: Worldwide clinical Trials Early Phase Services LLC, San Antonio, TX

The initial retention sample collected on 12-11-12 for Study #3006977 (Protocol BNX-110) consisted in part of 5 sealed boxes of Suboxone (buprenorphine and naloxone) Sublingual film, Lot C12GW104. You later allowed the Sponsor to collect one sealed box and a second open box from your retention sample on 2-23-13 thus leaving a total of 3 sealed boxes for your retention sample.

In their response, WCT maintained that they randomly selected and appropriately stored reserve samples in their original containers. They stated that part of the designated reserve samples was transferred to the sponsor on the sponsor's request and this transfer was documented. WCT believes that they did not violate FDA's regulation on reserve samples because they maintained sufficient quantities for FDA's requirements, after partial return of the reserves to the sponsor.

In our opinion, it was not appropriate on the sponsor's part to remove investigational products already assigned as reserve samples. However, the reserve samples kept at WCT did not get contaminated by introduction of substitute or other sponsor-handled products.

Because sufficient quantities of reserve samples were retained at WCT and submitted to the ORA Investigator at the inspection,

we recommend that these reserve samples are sufficient to establish the identity of the products dosed in Study BNX-110.

Conclusions:

Following the above inspection, we recommend that data for the clinical and analytical portions of study BNX-110 are acceptable for further agency review.

Arindam Dasgupta, Ph.D.
BE Branch, DBGLPC, OSI

Chase H. Bourke, Ph.D.
GLP Branch, DBGLPC, OSI

Final Classification:

VAI- WCT, San Antonio, TX (FEI 3006724658)

(b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Bonapace/Choi/Skelly/Dasgupta/Bourke/Dejernett

OSI/DBGLPC/Bonapace/Mada

CDER/OND/ODEII/DAAAP/Rappaport/Sullivan

ORA/SW-FO/DAL-DO/Ngai

ORA/SW-FO/DAL-DO/DAL-IB/SAN-TX/Martinez

Draft: AD 04/25/2014

Edit: MFS 4/25/14; SHH 4/25/14

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Analytical Sites/ (b) (4) /NDA 205-637 Buprenorphine and Naloxone buccal film

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/s/

ARINDAM DASGUPTA
04/28/2014

CHASE H BOURKE
04/28/2014

SAM H HAIDAR
04/28/2014

WILLIAM H TAYLOR
04/29/2014

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

Label, Labeling and Packaging Review

Date: March 7, 2014

Reviewer: Vicky Borders-Hemphill, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader: Irene Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Bunavail
(Buprenorphine and Naloxone buccal film)
[REDACTED] (b) (4) 2.1 mg/0.348 mg, 4.2 mg/0.696 mg,
6.3 mg/1.044 mg

Application Type/Number: NDA 205637

Applicant/Sponsor: Biodelivery Sciences International Inc

OSE RCM #: RCM # 2013-2021

*** This document contains proprietary and confidential information that should not be released to the public.***

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2	METHODS AND MATERIALS REVIEWED	2
3	MEDICATION ERROR RISK ASSESSMENT.....	2
4	CONCLUSIONS	4
5	RECOMMENDATIONS.....	4
	Appendices.....	7

1 INTRODUCTION

This review evaluates the proposed labels and labeling for Bunavail, NDA 205637, for areas of vulnerability that could lead to medication errors, in response to a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

1.1 PRODUCT INFORMATION

On August 7, 2013, the Sponsor submitted NDA 205637 for the maintenance treatment of opioid dependence. The following product information is provided in the October 25, 2013 insert labeling submission.

- Active Ingredient: buprenorphine and naloxone
- Indication of Use: maintenance treatment of opioid dependence.
- Route of administration: Buccal
- Dosage form: buccal film; each dosage unit is a yellow, rectangular film, with the mucoadhesive side of each film marked with a code ((b) (4) BN2, BN4, or BN6) corresponding to each unique strength.
- Strength: buprenorphine/naloxone: (b) (4) 2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg
- Dose: one buccal film daily
 - The recommended target dosage is (b) (4) mg buprenorphine/day as a single daily dose. The dosage should be progressively adjusted in increments/decrements of (b) (4) mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms. When two films are required, it is recommended that one film should be placed on the inside of each cheek. For other multiple film doses, it is recommended that no more than two films should be applied to a single side.
- How Supplied and Container/Closure System: Each buccal film is individually wrapped in a protective foil package that is (b) (4) sealed and child resistant. There are 30 individually wrapped films per carton. The cartons will be (b) (4) (b) (4) The cartons will use the same identifying color coding as will be used for the various dosage strengths on the individual foil packages. The different strengths will be distinguished by color coding on the individual foil packages.
- Storage: Store at 20 - 25°C (68 - 77°F), protected from freezing and moisture, until ready to use

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of human factors and Failure Mode and Effects Analysis,¹ to evaluate the following:

- Container (foil package) Labels submitted August 7, 2013 (Appendix B)
- Carton Labeling submitted August 7, 2013 (Appendix C)
- Medication Guide submitted August 7, 2013
- Prescribing Information submitted October 25, 2013
- Sample films submitted December 9, 2013
- Medication Error Reports from Clinical Study BNX-201 submitted December 10, 2013

3 MEDICATION ERROR RISK ASSESSMENT

Sample film and Medication Error Data from clinical study BNX-201

During the Bunavail team meeting on November 12, 2013, the team discussed the concern of proper film placement in the buccal cavity since the film has one side that has a mucoadhesive layer containing buprenorphine and the other side that has a nonmucoadhesive layer containing naloxone. DMEPA reviewed the sample films submitted December 9, 2013 and medication error data from clinical study BNX-201 to inform our assessment of medication error risk.

The sample films show that the film is semi-transparent with a unique identifier visible on both sides with one side showing a mirror image of the unique identifier. For dosing, the patients are instructed to place the text side against the inside of the mouth. Since the text is visible on both sides of the film, this may present confusion for the patient.

DMEPA reviewed medication error data from clinical study BNX-201 to determine if there were any reports related to improper placement resulting in complaints of decreased effectiveness. A listing of medication errors observed as a result of study drug non-compliance is provided in Appendix D. These reported medication errors are summarized below in Table 1.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Table 1: Summary of Medication Errors reported for 16 patients from Study BNX-201 (open label study to assess safety and tolerability of Bunavail in 249 opioid dependent subjects)	
Medication Error Type	n=22
Product Quality Issues (adhesion issues): difficulty applying (4); fell off (1); poor adherence (3); stick to dentures (1); did not stick (2)	11
Missed Dose: tore while removing from pouch (1); clumping/tore/stuck to finger (1); dropped film (1); balled up in fingers (2)	5
Improper Dose: forgot dose taken (1); patient had nausea and vomiting due to viral syndrome therefore took extra dose (1); extra dose because they get gummy (1)	3
Wrong Frequency of administration: twice daily administration	1
Wrong technique: cut film leading to underdose	1
Wrong route: swallowed	1

There were no reports indicating that improper film placement in the buccal cavity occurred resulting in complaints of lack of effectiveness. DMEPA defers to the clinical review team to determine if placement of the wrong side of the film in the buccal cavity can impact efficacy. If efficacy is affected by improper film placement, then we recommend a human factors usability study be conducted prior to approval.

We identified 11 cases of reported product quality issues relating to adhesion of the product; however, the root cause of the adhesion issues from Study BNX-201 could not be determined from the information provided. We defer to the Office of New Drug Quality Assessment (ONDQA) regarding adhesion assessment of this product.

Additionally, we identified other types of medication errors. Based on our findings, we provide recommendations for the labels and labeling of this product to minimize the risk for medication error.

Container Labels and Carton Labeling

The proposed product, Bunavail, is a multi-ingredient formulation of buprenorphine and naloxone proposed in four strengths ((b) (4) 2.1 mg/0.348 mg, 4.2 mg/0.696 mg, 6.3 mg/1.044 mg). However, there are two strength presentations on the principal display panel of the container labels and carton labeling. (b) (4)

(b) (4)

DMEPA is concerned that two different strength presentations on the container labels and carton labeling may be a source of confusion. (b) (4)

(b) (4) may lead to confusion when a healthcare professional is

selecting the intended strength during prescribing or dispensing. For example, (b) (4)

[REDACTED]

This could result in improper use of this product for unapproved indications (e.g. induction therapy) or at incorrect doses if it is believed that Bunavail is interchangeable with other buprenorphine single ingredient products. To mitigate the risk for medication errors, we recommend that there be only one statement of strength on the labels and labeling that reflects both active ingredient strengths accurately.

Medication error data from Study BNX-201 identified one case of the patient cutting the film resulting in an underdose. The Medication Guide instructs the patient to not cut or tear the film. However, this instruction is not included on the foil package label or the carton labeling. See Section 5 for recommendations to add instructions to the labels and labeling to not cut or tear the film.

Prescribing Information and Medication Guide

There are several instances throughout the insert labeling where two strength presentations are used. As discussed for the container and carton label and labeling above, we recommend a single statement of strength that reflects both active ingredient strengths accurately.

Additionally, the language in Section 2.2 (Method of Administration) of the Prescribing Information and under the “How Should I take Bunavail” section of the Medication Guide can be revised to improve readability of the dosing instructions for healthcare providers and patients. See Section 5 for recommended changes to these sections of the insert labeling and Medication Guide.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved for clarity and to increase the readability and prominence of important information to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of NDA 205637:

A. Comments to the Division

a. Prescribing Information: General Comments

- i. Remove the (b) (4) and use a single statement of strength that reflects both active ingredient strengths accurately at least out to the hundredths decimal place similar to the following:

[REDACTED] (b) (4)

b. Prescribing Information: Section 2.2 (Method of Administration)

- i. Revise the statement from “use their tongue to wet the inside of their cheek or rinse their mouth with water to moisten the area for placement of Bunavail” to read “use their tongue to wet the inside of their cheek or rinse their mouth with water to moisten the area immediately before placement of Bunavail”.
- ii. Revise the statement from “(b) (4) with the text (b) (4) BN2, BN4, or BN6) facing up” to read “pinch a corner of the film between two dry fingers with the text (b) (4) BN2, BN4, or BN6) facing up” to prevent dropping and losing the film during administration as was seen in medication error data from Study BNX-201 submitted December 10, 2013.
- iii. Revise the statement from “(b) (4), to read “When two films are required for one dose, place one film on the inside of one cheek and the other film on the inside of the other cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time.”
- iv. Add the statement “Use the entire film. Do not cut or tear Bunavail”.

c. Medication Guide (“How Should I Take Bunavail” section)

- i. See comments A.b.i. through A.b.iv. above.
- ii. Add a corresponding image to demonstrate the application of one film per cheek (see A.b.iii. above)
- iii. Revise the statement “(b) (4)” to read “Do not cut or tear Bunavail”

B. Comments to the Applicant

a. Foil package Labels

- i. Remove the (b) (4) since it is not considered an accurate representation of the actual strength. We recommend using a single statement of strength that reflects both active ingredient strengths accurately at least to the second decimal place (the hundredth) similar to the following:

(b) (4)

Additionally, increase the font size of the statement of strength for increased prominence.

- ii. Increase the font size of the established name to ensure that the established name is half the size of the proprietary name as required per *21 CFR 201.10(g)(2)*.

iii. Revise the statement “^{(b) (4)}” to read “Use entire film. Do not cut, tear, chew, or swallow film”. Relocate this statement from the back panel to the principal display panel for increased prominence of this important information. To accommodate this, consider moving the statements “Keep out of reach...medical care.” and the URL address (www.Bunavail.com) to the back panel.

b. Carton Labeling

- i. See recommendation B.a.i and B.a.ii above.
- ii. Add the statement “Use entire film. Do not cut, tear, chew, or swallow film” to the principal display and back panels.

If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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Appendix D: Medication Error Data from Study BNX-201 submitted December 10, 2013

1.11.3 Response to FDA Request for Information – Efficacy

NDA 205637 SN0011

Table 1 Medication Errors Observed as a Result of Study Drug Non-compliance

Subject Number	Gender	Age (years)	Study Day	Description Provided by the Subject	Subject's Assessment of Ease of Use
01-0026	M	28	7	Subject had difficulty applying the films and used 2 extra films as replacements.	Difficult to use
			14	Subject tore 1 film while opening the packet; it was not used and not returned.	
01-0029	M	28	7	Subject used 3 extra films of study drug. Reasons were: 1 clumped, 1 tore, and 1 stuck to finger during application. These 3 films were discarded.	Easy to use
			14	Subject used 3 extra films of study drug. Reasons were that they fell off after application and so they were replaced.	
01-0033	F	34	ET	Subject reported using 1 extra dose of study drug due to poor adherence to the oral mucosa.	Difficult to use
02-2017	M	39	7	Subject misunderstood dosing and was taking study drug twice daily. Subject was re-educated regarding dosing.	Unavailable
02-2071	M	46	7	Subject reported using extra study drug as replacements for films that stuck to his dentures.	Very easy to use
02-2098	M	28	ET	Subject reported having difficulty using the films. Subject had no complaints of associated adverse events.	Unavailable
02-2152	F	41	14	Subject reported that extra films were used due to nonadherence of films. Subject was re-instructed on application.	Very easy to use
03-3021	F	31	7	Subject cut a film in half and took a half of a film.	Very easy to use
03-3030	M	32	7	Subject reports that they forgot if they dosed so he took another dose.	Unavailable
05-5034	F	37	7	Subject stated 1 film was dropped and 1 film got wet before application, so both were discarded.	Very easy to use
07-7005	M	38	42	Subject used extra drug because they had a viral syndrome and worried that the films were not absorbing due to nausea and vomiting.	Difficult to use

Subject Number	Gender	Age (years)	Study Day	Description Provided by the Subject	Subject's Assessment of Ease of Use
07-7023	M	50	42	Subject reports using extra study drug because they get gummy and the subject was worried that they were not working. Also, reports that some films were swallowed.	Very easy to use
08-8042	M	41	42	Subject reported that 1 film did not stick.	Easy to use
10-1001	F	32	7	Subject reported that films sometimes "balled up in fingers" so she replaced these and didn't return the "used" study drug.	Unavailable
10-1007	M	24	7	Subject reported that films sometimes "balled up in fingers" so he replaced these and didn't return the "used" study drug.	Difficult to use
			14	Subject reports having problems with films not sticking to the mucosa and having to be replaced.	
10-1017	M	34	7	Subject having difficulty attaching films.	Very difficult to use
			14	The subject still reported having difficulty with application.	
			56	Subject reported poor adhesion.	

ET: early termination

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

/s/

BRENDA V BORDERS-HEMPHILL
03/07/2014

IRENE Z CHAN
03/10/2014