

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**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**

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date: October 23, 2015

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Drug Name(s): Belbuca (buprenorphine hydrochloride buccal film)

Therapeutic Class: Opioid agonist

Dosage and Route: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg,
and 900 mcg buccal film

Application Type/Number: NDA 207932

Submission Number: Sequence No. 0000

Applicant/sponsor: Endo Pharmaceuticals, Inc.

OSE RCM #: 2015-2626; 2015-2628

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

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EXECUTIVE SUMMARY

The purpose of this review is to document Division of Risk Management's (DRISK's) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Belbuca (buprenorphine hydrochloride) buccal film. Endo Pharmaceuticals Inc. (Endo) originally submitted NDA 207932 on December 23, 2014, and last amended on October 23, 2015, under section 505 (b) (2) using NDA 18401, Buprenex (buprenorphine solution), and ANDA 78633, sublingual tablets, as the reference listed drugs.

If approved, Belbuca's risks of abuse/misuse, addiction, overdose and death can be mitigated with labeling and a REMS. DRISK recommends Endo be required to join the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS for Belbuca.¹

1 INTRODUCTION

The purpose of this review is to document Division of Risk Management's (DRISK's) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Belbuca [buprenorphine hydrochloride (HCl)] buccal film. Endo Pharmaceuticals Inc. (Endo) submitted NDA 207932 on December 23, 2014, and last amended on October 23, 2015, under section 505 (b) (2) using NDA 18401, Buprenex (buprenorphine HCl solution), and ANDA 78633, sublingual (SL) tablets, as the reference listed drugs (RLD). The amended NDA submission for Belbuca included a proposed REMS document, including appended materials, and REMS supporting document based on the Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA Opioid REMS) (approved October 2, 2015).

1.1 PRODUCT BACKGROUND

Buprenorphine is a synthetic opioid that is classified as a μ -opioid receptor partial agonist and a Schedule III controlled substance in the United States. The analgesic efficacy of buprenorphine is mediated by its high-affinity binding to, and very slow rate of dissociation from, μ -opioid receptors in the central nervous system. Buprenorphine is considered a long-acting opioid analgesic because it has a longer period of action based on the inherent characteristics of the drug substance, which stays longer in the body.

Belbuca (buprenorphine HCl buccal film), is buprenorphine HCL in a buccal film dosage form. Belbuca (buprenorphine HCl buccal film), a transmucosal form of buprenorphine, is designed to enable buccal absorption of buprenorphine, therefore, bypassing gastrointestinal absorption and first pass metabolism. Endo submitted the NDA under section 505 (b) (2) using NDA 18401, Buprenex (buprenorphine solution), and ANDA 78633, sublingual tablets, as the RLD. If approved, Belbuca will be available as 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg buccal film indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The Belbuca buccal film is formulated to deliver the active ingredient over 12 hours.

¹ Details of the regulatory history, development, and rationale for the design of the REMS and REMS materials of the ER/LA Opioid Analgesic REMS are discussed in the Executive Memorandum, dated July 6, 2012.

Belbuca is the first buccal film formulation of buprenorphine which is seeking approval for the above indication. Other formulations of buprenorphine are currently approved for the treatment of opioid addiction or pain. The following formulations are approved for the treatment of opioid addiction.

- SL tablets (Subutex and generics),
- SL tablets, in combination with naloxone (Zubsolv, Suboxone, and generics),
- SL film, in combination with naloxone (Suboxone SL film), and
- Buccal film, in combination with naloxone (Bunavail).

The following formulations are approved for the treatment of pain:

- intravenous or intramuscular solution for injection (Buprenex and generics): approved for the relief of moderate to severe pain
- transdermal patch (Butrans): approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and is a member of the ER/LA Opioid REMS.

The ER/LA Opioid REMS was approved with the following elements:

- Medication Guide (MG)
- Elements to assure safe use
 - Prescriber Training
 - FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint)
 - Patient Counseling Document (PCD) on Extended-Release and Long-Acting Opioid Analgesics
 - Letters to DEA-Registered Prescribers
 - Letters to Professional Organizations/Licensing Boards
 - REMS website
- Timetable for Submission of Assessments

1.2 REGULATORY HISTORY

December 23, 2014: Endo submitted an NDA 207932 for Belbuca as a 505(b) (2) application using Buprenex (buprenorphine HCl solution; NDA 18401) and buprenorphine HCl SL tablets (ANDA 78633) as the RLDs. The NDA submission for Belbuca included a proposed REMS document, including appended materials, and REMS supporting document based on the Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA Opioid REMS) (approved on August 19, 2014).

June 26, 2015: The Agency approved a revised version of the ER/LA Opioid REMS.

October 20, 2015: The Agency communicated, via email, DRISK's comments on the Sponsor's proposed REMS for Belbuca.²

October 22, 2015: The Sponsor amended the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* (FDA Blueprint) based on the

² Gonzalez D. DRISK REMS Review for Belbuca. dated October 20, 2015.

comments provided by the Agency. The Sponsor did not include the other REMS documents with the submission.

October 23, 2015: The amended submission received on October 22, 2015 was not considered by the Agency to be a complete REMS submission; therefore, the Agency requested that the Sponsor amend the submission to include all requested documents (i.e., the REMS document, including appended materials, and REMS supporting document). The Sponsor amended the proposed REMS for Belbuca to include the REMS document, appended materials, and REMS supporting document. These materials are the focus of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 207932 for the proposed ER/LA Opioid REMS:

- Endo Pharmaceuticals, Inc. Proposed REMS for Belbuca, NDA 207932, received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000).
 - Amendment received October 22, 2015 (eCTD Seq. No. 0024)
 - Amendment received October 23, 2015 (eCTD Seq. No. 0025)

2.2 MATERIALS INFORMING OUR REVIEW

The following is a list of materials that were used to inform this review:

- Endo Pharmaceuticals, Inc. Draft Prescribing Information for Belbuca. received April 21, 2015 (ORIG-1; eCTD Seq. No. 0008)
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on June 26, 2015.
- Horn P. Clinical Review and Evaluation for Belbuca, dated September 9, 2015.
- Walker M. Patient Labeling Review for Belbuca, dated August 2, 2015.
- Randall-Thompson J. Controlled Substance Staff Review for Belbuca, dated August 27, 2015.
- Liu J. QT-Interdisciplinary Review Team (IRT) Review for Belbuca, dated June 18, 2015.
- Gonzalez D. DRISK REMS Review for Belbuca, dated October 20, 2015.

3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

3.1 Summary of Efficacy

The efficacy of Belbuca from 2 placebo-controlled Phase 3 clinical studies (Study EN3409-307 and EN3409-308) was used to support the proposed submission. The efficacy results of these individual studies and of the pooling of data from these studies provide an overall analysis of the integrated efficacy results.

3.1.1 Efficacy of Belbuca for the management of pain

EN3409-307 ($n_{\text{Belbuca}} = 254$; $n_{\text{placebo}} = 256$) was a multicenter, double-blind, placebo-controlled, enriched enrollment, randomized withdrawal study comparing Belbuca to placebo buccal film in opioid-experienced subjects with moderate to severe chronic lower back pain (CLBP) requiring continuous opioid analgesia for an extended period of time. The primary objective of the study was to determine the analgesic efficacy of Belbuca every 12 hours in opioid-experienced subjects with moderate to severe CLBP requiring continuous opioid analgesia for an extended period of time. The secondary efficacy objectives were to determine the analgesic efficacy of Belbuca every 12 hours and to evaluate the impact of Belbuca every 12 hours on daily function parameters using patient-reported outcome (PRO) measures.

Based on the Sponsor's analysis of EN3409-307, treatment with Belbuca resulted in a statistically significant treatment difference compared with placebo in mean change from double-blind baseline to week 12 in average daily pain intensity scores, with a least squares mean treatment difference of -0.98 (95% CI, -1.32 to -0.64) for the intention to treat (ITT) population. In addition, a treatment difference favoring the Belbuca group compared with the placebo group was observed at each week in the double-blind treatment phase for the ITT population.

EN3409-308 ($n_{\text{Belbuca}} = 229$; $n_{\text{placebo}} = 232$) was a multicenter, double-blind, placebo-controlled, enriched enrollment, randomized withdrawal study comparing Belbuca to placebo buccal film. The primary objective was to determine the analgesic efficacy of Belbuca every 12 hours in opioid-naïve subjects with moderate to severe CLBP requiring continuous around the clock opioid analgesia for an extended period of time. Secondary objectives were to determine the safety, tolerability, and analgesic efficacy of Belbuca every 12 hours and to evaluate the impact of Belbuca every 12 hours on daily function parameters using PRO measures.

Based on the Sponsor's analysis of EN3409-308, the treatment with Belbuca resulted in a statistically significant treatment difference compared with placebo in mean change from double-blind baseline to week 12 in average daily pain intensity scores, with a mean treatment difference of -0.67 (95% CI, -1.07 to -0.26; $P < 0.0012$) for the ITT population. A treatment difference favoring the Belbuca group compared with the placebo group was observed at each week in the double-blind treatment phase for the ITT population.

The clinical reviewer has concluded that the Applicant has demonstrated efficacy in two trials compared to placebo (studies EN3409-307 and EN3409-308). The reviewer stated, "The primary efficacy analysis, an analysis of covariance of the change from Baseline to Week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores (using an 11-point NRS), is not novel and the key secondary efficacy analyses (proportion of subjects that achieved 30% and 50% pain reduction) support the primary findings and are also not novel." In addition, both opioid-naïve and opioid-experienced populations were studied. The Sponsor demonstrated efficacy in both populations. The reviewer³ also reported that "the treatment effect observed is generally within the range observed for other opioid analgesics." ⁴

³ Gonzalez D. DRISK REMS Review for Belbuca. dated October 20, 2015.

3.2 SUMMARY OF SAFETY

The evaluation of safety in patients is primarily based on the 3 Phase 3 studies, which included Study BUP-301, EN3409-307, and EN3409-308 and supported with additional data from 2 open-label, long-term safety studies (BUP-305 and EN3409-309). Study BUP-301 evaluated the efficacy and safety of buprenorphine HCl buccal film doses ranging from 60 to 240 µg in a population of subjects with CLBP, who were either opioid naïve or opioid experienced, in a double-blind, placebo-controlled, enriched enrollment, randomized withdrawal study. However, the efficacy endpoint was not met so this study was only used to collect safety data. In addition, BUP-305 and EN3409-309 were both uncontrolled open-label, long-term safety studies in subjects with moderate to severe chronic pain. The clinical reviewer pooled all the data described in these studies to assess the safety profile for Belbuca.⁴ The integrated safety analysis set of data consisted of all patients (n = 2127) who took at least 1 dose of Belbuca in the aforementioned studies. In addition, QT prolongation was studied in trial BUP-150 (discussed separately below). The majority of safety concerns observed in these studies were consistent with the expected adverse reactions associated with the drug class.

The clinical reviewer⁴ reported that "there were no new safety concerns for buprenorphine in a pain population identified in the development program safety database. From this pooled data, there were few serious adverse events, and the common adverse events are consistent with what is already known about buprenorphine and opioids in this treatment setting." The reviewer concluded that, based on the current data, the safety concerns with Belbuca do not outweigh the benefits of the drug. In addition, the Controlled Substance Staff (CSS) reviewer⁵ found that there were "no measureable differences in the abuse-related adverse event profiles of Belbuca buccal film in comparison to other marketed buprenorphine products." The CSS reviewer recommended language in the product label describing the risks of abuse and dependence in both section 9.0 (*Drug Abuse and Dependence*) and the boxed warning which would remain the same as currently written in the existing labels for Butrans and other buprenorphine products indicated for pain.

There were no deaths attributed to the use of Belbuca in the development program. There was one death in the development program in open-label safety study 305; however, it was considered unrelated to Belbuca.

There were 88 nonfatal serious adverse events in 69 subjects. This accounted for 3% of subjects having a nonfatal serious adverse event in all Phase 3 studies. The clinical reviewer noted that most of the serious adverse events that occurred were unlikely to be related to Belbuca. In addition, the clinical reviewer stated that for serious adverse events that could have been related to Belbuca "no novel safety signals arose" during the safety studies.⁶

⁴ Horn P. Clinical Review and Evaluation for Belbuca, dated September 9, 2015.

⁵ Randall-Thompson J. Controlled Substance Staff Review for Belbuca, dated August 27, 2015

Effects of Belbuca on QT/QTc

(b) (4)

The Sponsor originally assessed QT/QTc effects of Belbuca Study BUP-150. BUP-150 was a double-blind, placebo- and positive-controlled, randomized, 4-period crossover, single-dose thorough QT/QTc study in healthy subjects to evaluate the effects of Belbuca on cardiac repolarization as measured by the surface electrocardiogram (ECG) QTc interval. Oral naltrexone was co-administered to protect the subjects from potential opioid-induced adverse events. The Sponsor reported that in all Phase 3 studies that the study medication had minimal effect on the QTc interval. However, the Agency clinical reviewer⁶ states that study BUP-150, which included the administration of naltrexone, has caused the study to be uninterpretable. Naltrexone is known to interfere with the effect of buprenorphine on cardiac repolarization. Due to this discrepancy, the clinical reviewer consulted with the QT-IRT reviewers to estimate the expected QT prolongation for Belbuca.

Based on the QT-IRT's analysis, Belbuca had an expected QT prolongation, at the highest proposed strength of 900 mcg every 12 hours, to be between 5 and 10 milliseconds, which is considered to be modest QT prolongation. The clinical reviewer noted that this result warranted additional language in the dosing and administration section of the Belbuca Prescribing Information (PI) advising prescribers not to exceed the 900 mcg every 12 hours dose and a warning advising prescribers not to use the product in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA or III antiarrhythmic medications.

4 RATIONALE FOR A REMS FOR BELBUCA

DRISK agrees with the Sponsor that a REMS is needed to ensure that the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse for Belbuca. While all opioid formulations have the potential for these risks, based on currently available data, the Agency believes that ER/LA opioids pose a higher risk for the aforementioned safety concerns than immediate-release opioid formulations because they contain more opioid per tablet, capsule, or patch and/or either stay in the body longer or are released into the body over longer periods of time. Additionally, when the extended-release features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an immediate-release

⁶ Horn P. Clinical Review and Evaluation for Belbuca, dated September 9, 2015.

manner, potentially resulting in overdose or death. Therefore, the ER/LA Opioid Analgesic REMS was developed and approved to mitigate these risks.

Belbuca will be the second opioid to join the ER/LA Opioid REMS because of the long-acting properties of the active ingredient; Butrans (buprenorphine) was the first long-acting product included in the ER/LA REMS. Belbuca's active ingredient, buprenorphine, may be associated with potentially serious safety issues of abuse, misuse, overdose and death. Buprenorphine has high affinity binding to, and slow dissociation from, mu opioid receptors, which make it long-acting compared to most other opioids. As a long-acting opioid, the class-wide REMS for ER/LA opioid analgesics is necessary and appropriate for this product to mitigate the risks of overdose, abuse, misuse, and addiction and to maintain a favorable risk-benefit profile for the product. In addition, the clinical reviewer concurred with this recommendation in her review.⁷

If approved Belbuca's risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse can be mitigated with labeling and a REMS. It is appropriate for Belbuca to join the single, shared system ER/LA Opioid REMS.

5 RESULTS OF REVIEW OF THE PROPOSED REMS FOR BELBUCA

The Sponsor proposed to incorporate Belbuca into the approved ER/LA Opioid REMS. This modification impacted the ER/LA Opioid REMS materials including the FDA Blueprint, the Prescriber Letters, the ER/LA Opioid Analgesic REMS website, and the REMS supporting document. DRISK reviewed Endo's proposed REMS, received on October 23, 2015, in response to comments from the Agency provided on October 21, 2015⁸.

5.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received October 23, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.1.1 Medication Guide

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Belbuca MG under separate cover and has communicated their recommendations to DAAAP. OPDP/PLRT has found the MG submission to be acceptable with their recommended changes.⁹

⁷ Horn P. Clinical Review and Evaluation for Belbuca, dated September 9, 2015.

⁸ Gonzalez D. DRISK REMS Review for Belbuca. dated October 20, 2015.

⁹ Walker M. Patient Labeling Review for Belbuca, dated August 2, 2015.

5.1.2 REMS Appended Materials

5.1.2.1 Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics

The Sponsor's proposal, received October 23, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.1.2.2 FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

The Sponsor proposed to include Belbuca product-specific language in the FDA Blueprint. DRISK finds the proposed changes received October 23, 2015, that incorporate the Agency's feedback as well as the additional language proposed by the Sponsor (see below) acceptable.

Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days.

5.1.2.3 Prescriber Letters

The Sponsor proposed to include Belbuca product-specific language in the Prescriber Letters. DRISK finds the proposed changes received October 23, 2015, that incorporate the Agency's feedback acceptable.

5.1.2.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, originally received October 23, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.1.2.5 ER/LA Opioid Analgesic REMS website

The Sponsor proposed to include Belbuca product-specific language on the REMS Website. DRISK finds the proposed changes received October 23, 2015, that incorporate the Agency's feedback acceptable.

5.1.3 Timetable for Submission of Assessments

The Sponsor's proposal, received October 23, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.2 REMS SUPPORTING DOCUMENT

The Sponsor proposed to include Belbuca product-specific language in the REMS supporting document to align with the proposed changes in the REMS. DRISK finds the proposed REMS supporting document, received October 23, 2015, that incorporate the Agency's feedback acceptable.

6 DISCUSSION AND CONCLUSION

A REMS for Belbuca is necessary to ensure the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from

inappropriate prescribing, misuse, and abuse for Belbuca. DRISK agrees with the Sponsor's proposal to include Belbuca within the ER/LA Opioid REMS.

The Sponsor submitted a proposed REMS for Belbuca on October 23, 2015 based on the Agency's comments. DRISK finds the proposed ER/LA Opioid REMS (attached) acceptable; therefore, DRISK recommends approval of the REMS as appended to this review.

7 RECOMMENDATION

DRISK recommends approval of the ER/LA Opioid REMS for Belbuca (buprenorphine hydrochloride buccal film) (NDA 207932), received October 23, 2015 and as appended to this review.

A REMS Modification Notification Letter should be sent to the other members of the ER/LA Opioid REMS to request the inclusion of these changes in their respective REMS.

8 ATTACHMENTS

Extended-Release and Long-Acting Opioid Analgesic REMS document and appended materials

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/s/

DANNY S GONZALEZ
10/23/2015

REEMA J MEHTA
10/23/2015
I concur.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA #:	207932
Product:	Belbuca (buprenorphine hydrochloride) buccal film
SPONSOR:	Endo Pharmaceuticals, Inc.
FROM:	Judith A. Racoosin, MD, MPH
DATE:	October 22, 2015

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

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

The use of prescription opioid drug products has nearly doubled in the past decade, and with that increase in use, there has been a concordant rise in the abuse and misuse of prescription opioid drug products, resulting in increased reports of serious adverse outcomes such as addiction, unintentional overdose, and death. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling, as well as inappropriate patient behaviors such as improper use, storage, and disposal of prescription opioid products. Extended-release and long-acting (ER/LA) opioid analgesic formulations pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. The amount of opioid contained in an extended-release tablet can be much more than the amount of opioid contained in an immediate-release tablet because extended-release tablets are designed to release the opioid over a longer period of time. Long-acting opioids can take many hours to be cleared out of the body. Improper use of any opioid can result in serious side effects including overdose and death, and this risk is magnified with ER/LA opioid analgesics. Because it is important that these products are prescribed and used safely among the intended population, FDA has determined that a REMS is necessary to address the issues of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics.

After consultations with the Office of New Drugs, the Office of Surveillance and Epidemiology, and members of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management committees in July 2010, we have determined that a class-wide REMS is necessary to ensure that the benefits of ER/LA opioid analgesics outweigh their risks. In reaching this determination, we considered the following:

- A. Approximately 24-33% of Americans suffer from chronic, non-cancer pain such as arthritis, lower back pain, and fibromyalgia. In year 2009, an estimated 3.8 million unique patients received a dispensed prescription for an ER/LA opioid analgesic product from outpatient retail pharmacies.
- B. ER/LA opioid analgesic products are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The majority of use for ER/LA opioid analgesic products is associated with “diseases of the musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain.
- C. ER/LA opioid analgesic products are an important part of the armamentarium of drugs used to treat chronic pain. Some advantages of these types of formulations over the short-acting opioids are: 1) less frequent dosing; 2) better control of pain achieved through more stable drug levels; 3) improved patient compliance; and 4) fewer opioid side-effects. It is important to note that patients respond differently to different opioid drug substances, and some patients develop tolerance to an opioid after chronic exposure. Physicians use a technique known as “opioid rotation” whereby they switch patients from one opioid to another if patients develop tolerance and cannot get adequate pain relief from any given opioid. Therefore, having different opioid analgesics available as modified-release formulations provides important pain relief options for these patients.
- D. The expected duration of treatment with ER/LA opioid analgesics will be from weeks to months or longer. Data from outpatient prescription claims databases suggest that ER/LA opioid analgesics are typically prescribed for approximately 30-days at a time, whereas immediate-release opioid products are prescribed for 13-21 days at a time.
- E. ER/LA opioid analgesic products have distinguished themselves among the class of opioid pain medications with their disproportionately high rate of serious adverse outcomes including addiction, unintentional overdose, and death, in comparison to immediate-release opioid analgesic products. The goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to these medications. Serious adverse outcomes of concern including addiction, unintentional overdose, and death have been reported for each of the ER/LA opioid analgesics.

F. ER/LA opioid analgesic products contain one of the following active drug substances: morphine, oxycodone, hydrocodone, fentanyl, buprenorphine, methadone, hydromorphone, oxymorphone, or tapentadol; none of these active drug substances are new molecular entities.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ER/LA opioid analgesic products pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ER/LA opioid analgesic products. FDA has determined that ER/LA opioid analgesics are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, ER/LA opioid analgesic products for which patient labeling could help prevent serious adverse events related to the use of these products.

The elements of the REMS will be a Medication Guide, Elements to Assure Safe Use, and a timetable for submission of assessments of the REMS.

The ER/LA opioid analgesic single shared system REMS was approved on July 9, 2012. Upon approval, Belbuca will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
10/22/2015

**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**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: October 21, 2015

Reviewer(s): Danny S. Gonzalez, Pharm. D., M.S.,
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Acting Deputy Director: Reema Mehta, Pharm. D., M.P.H.
DRISK

Drug Name(s): Belbuca (buprenorphine hydrochloride buccal film)

Therapeutic Class: Opioid agonist

Dosage and Route: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg,
and 900 mcg buccal film

Application Type/Number: NDA 207932

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1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of Endo Pharmaceuticals, Inc. (Endo) REMS submission, received from Endo on December 23, 2014 (ORIG-1; eCTD Seq. No. 0000). Endo is submitting an NDA under section 505(b)(2) using NDA 18401, Buprenex (buprenorphine solution), and ANDA 78633, sublingual tablets, as the reference listed drugs (RLD). The Sponsor is currently a member in the REMS Program Companies (RPC). On December 23, 2014, Endo submitted a proposed REMS which included Belbuca in the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* of the ER/LA REMS. This submission is the focus of this review.

1.1 PRODUCT BACKGROUND

Buprenorphine is a synthetic opioid that is classified as a μ -opioid receptor partial agonist and a Schedule III controlled substance in the United States. The analgesic efficacy of buprenorphine is mediated by its high-affinity binding to, and very slow rate of dissociation from, μ -opioid receptors in the central nervous system (CNS). These attributes contribute to the unique pharmacologic profile of buprenorphine. Buprenorphine is considered a long-acting opioid analgesic because it has a longer period of action based on the inherent characteristics of the drug substance, which stays longer in the body, and not because of special design features of the finished product like those found in the extended-release opioids.

Belbuca (buprenorphine HCl buccal film), is buprenorphine HCL in a buccal film dosage form. Belbuca (buprenorphine HCl buccal film), a transmucosal form of buprenorphine, is designed to enable buccal absorption of buprenorphine, bypassing gastrointestinal absorption and first pass metabolism. Endo Pharmaceuticals Inc. (Endo) is submitting an NDA under section 505 (b) (2) using NDA 18401, Buprenex (buprenorphine solution), and ANDA 78633, sublingual tablets, as the reference listed drugs (RLD). If approved, Belbuca will be available as 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg buccal film indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Belbuca is the first buccal film formulation of buprenorphine which is seeking approval for a pain indication. Other formulations of buprenorphine are approved for pain. An injectable (intravenous or intramuscular) buprenorphine product (Buprenex and generics) is approved by the FDA for the relief of moderate to severe pain. Buprenorphine is also available as a transdermal patch (Butrans) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and is a member of the ER/LA REMS.

Other buprenorphine products, in multiple formulations and combinations with naloxone, are available for the treatment of opioid addiction. Buprenorphine is available as:

- Sublingual (SL) tablets (Subutex and generics),
- SL tablets (Zubsolv, Suboxone, and generics),
- SL film (Suboxone SL film), and

- Buccal film (Bunavail).

As an extended-release Schedule III opioid analgesic, Belbuca poses a risk of abuse/misuse, tolerance, dependence and withdrawal syndrome. If approved, Belbuca's risks of abuse/misuse, addiction, overdose and death can be mitigated with labeling and a REMS. DRISK recommends Endo Pharmaceuticals, Inc. be required to join the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA REMS) for Belbuca.¹

The ER/LA opioid analgesics SSS REMS was approved with the following elements:

- Medication Guide
- Elements to Assure Safe Use
 - Prescriber Training
 - FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint)
 - Patient Counseling Document (PCD) on Extended-Release and Long-Acting Opioid Analgesics
 - Letters to DEA-Registered Prescribers
 - Letters to Professional Organizations/Licensing Boards
 - REMS website
- Timetable for Submission of Assessments

1.2 REGULATORY HISTORY

December 23, 2014: Endo submitted an NDA 207932 for Belbuca as a 505(b)(2) application (ORIG-1; eCTD Seq. No. 0000) using Buprenex ((buprenorphine hydrochloride solution); NDA 18401) and buprenorphine hydrochloride sublingual tablets (ANDA 78633) as the reference listed drugs. The NDA submission for Belbuca included a proposed REMS Document, appended materials and the REMS Supporting document based on the ER/LA Opioid Analgesic REMS (August 2014).

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 207932 for the proposed ER/LA Opioid Analgesics REMS:

- Endo Pharmaceuticals, Inc. New Drug Application 207932, December 23, 2014 (ORIG-1; eCTD Seq. No. 0000).

2.2 MATERIALS INFORMING OUR REVIEW

¹ Details of the regulatory history, development, and rationale for the design of the REMS and REMS materials of the ER/LA Opioid Analgesic REMS are discussed in the Executive Memorandum, dated July 6, 2012.

- Endo Pharmaceuticals, Inc. Draft Prescribing Information for Belbuca. Submitted April 21, 2015 (ORIG-1; eCTD Seq. No. 0008)
 - FDA revised, Draft Prescribing Information for Belbuca. Emailed to the Sponsor the week of October 12, 2015.
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on June 26, 2015.
- Horn P. Clinical Review and Evaluation for Belbuca, September 9, 2015.
- Randall-Thompson J. Controlled Substance Staff Review for Belbuca, August 27, 2015.
- Liu J. QT-Interdisciplinary Review Team (IRT) Review for Belbuca, June 18, 2015.
- Walker M. OPDP/Patient Labeling Review Team Review for Belbuca, August 2, 2015.

3 DRISKS'S EVALUATION OF THE PROPOSED REMS

3.1 MEDICATION GUIDE

The OPDP/Patient Labeling Review Team's (LRT) has reviewed the Sponsor's proposed Belbuca Medication Guide (MG) under separate cover and has communicated their recommendations to DAAAP. OPDP/Patient LRT has found the MG submission to be "acceptable."

3.2 REMS DOCUMENT

The Sponsor's proposed REMS document, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) has no additional changes; therefore, DRISK finds them acceptable.

3.3 APPENDED MATERIALS

3.3.1 Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) has no additional changes; therefore, DRISK finds them acceptable.

3.3.2 FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) incorporates the Belbuca product-specific information throughout the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.

DRISK General Comments: DRISK and DAAAP have reviewed the Sponsor's submission, from December 23, 2014, and recommend the changes summarized

below. The Agency's agreed upon document is appended to this review. Overall, the Agency's proposed changes to the Sponsor's submission align the document with the ER/LA REMS goals as well as the Belbuca Prescribing Information.

Agency Comments for Section IV.f:

f. (b) (4)

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission. (b) (4)

Agency Proposal for Section V.h:

h. For buccal film products, the film should not be applied if it is cut, damaged, or changed in any way. Use the entire film.

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission. This recommended change to Section V.h clarifies (b) (4)
the need to use the entire buccal film products.

Agency Proposal for Section VI:

* Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) Belbuca (buprenorphine (b) (4) buccal film) Butrans (buprenorphine transdermal system) Dolophine (methadone HCl tablets) Duragesic (fentanyl transdermal system) Embeda (morphine sulfate ER-naltrexone capsules) Exalgo (hydromorphone HCl ER tablets) Hysingla ER (hydrocodone bitartrate ER tablets) Kadian (morphine sulfate ER capsules)	MorphaBond (morphine sulfate ER tablets) MS Contin (morphine sulfate ER tablets) Nucynta ER (tapentadol HCl ER tablets) Opana ER (oxymorphone HCl ER tablets) OxyContin (oxycodone HCl ER tablets) Targiniq ER (oxycodone HCl/naloxone HCl ER tablets) Zohydro ER (hydrocodone bitartrate ER capsules)
Dosing Interval	Refer to individual product information.

DRISK Comment: DRISK and DAAAP have reviewed the Sponsor's submission. This proposed edit aligns with the current prescribing information for Belbuca.

Agency Proposal for Section VI. Key Instructions section:

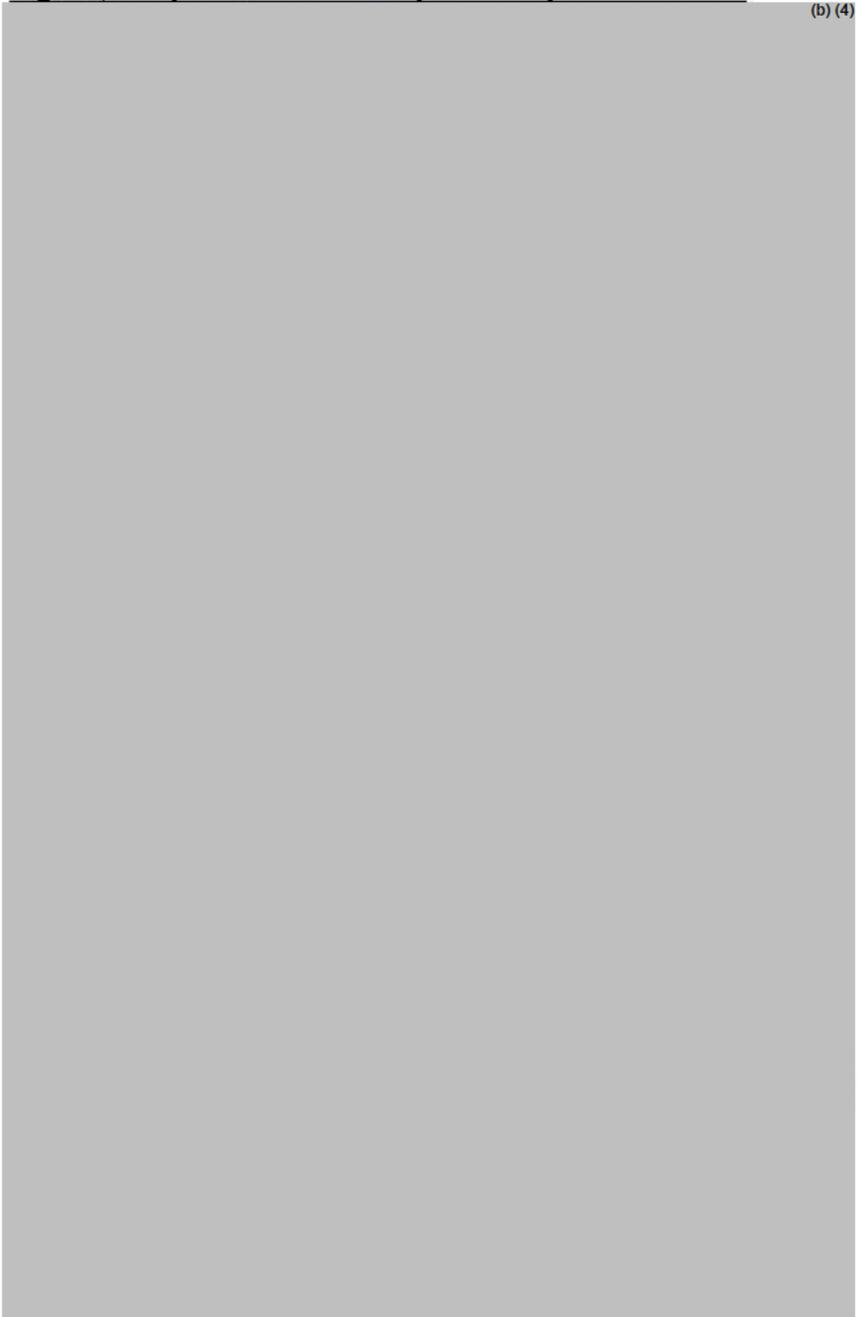
- Buccal film dosage from:
 - Do not use if the package seal is broken or the film is cut, damaged, or changed in any way.

(b) (4)

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission. The proposed changes to the Sponsor's submission align the document with the ER/LA REMS goals as well as the Belbuca Prescribing Information.

Agency Proposal for Belbuca product-specific section:

(b) (4)



DRISK Comments: RISK and DAAAP have reviewed the Sponsor's submission and recommend the changes summarized above for Belbuca's product-specific entry in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. The proposed changes to the Sponsor's

submission aligns the Belbuca product-specific information with the ER/LA REMS goals as well as the Belbuca Prescribing Information.

3.3.3 Prescriber Letters

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) added the term "buprenorphine-containing buccal films" to Prescriber letter #3.

DRISK Comments: RISK and DAAAP have reviewed the Sponsor's submission and do not find this change acceptable. DRISK recommends the following language. This recommendation clarifies that this statement only refers to buccal films that are indicated for use as analgesics.

The branded and generic drug products subject to this REMS include all:

- extended-release, oral-dosage forms containing
 - hydrocodone,
 - hydromorphone,
 - morphine,
 - oxycodone,
 - oxymorphone, or
 - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
(b) (4)
- methadone tablets and solutions *as well as buprenorphine-containing buccal films* that are indicated for use as analgesics.

3.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) has no additional changes; therefore, DRISK finds them acceptable.

3.3.5 ER/LA Opioid Analgesic REMS website

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) added the terms "buprenorphine-containing buccal films" and "buccal film" to *Selected Important Safety Information* section of the website (see below).

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission and do not find this change acceptable. DRISK recommends the following language to be included in the Selected Important Safety Information in the ER/LA website. This will clarify that this statement only refers to buccal films that are indicated for use as analgesics and will align with the message in Prescriber letter #3 (see above).

Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
 - hydrocodone,
 - hydromorphone,
 - morphine,
 - oxycodone,
 - oxymorphone, or
 - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; and
(b) (4)
- methadone tablets and solutions [as well as buprenorphine-containing buccal films](#) that are indicated for use as analgesics.

3.4 REMS SUPPORTING DOCUMENT

The Sponsor's proposal, originally received December 23, 2014 (ORIG-1; eCTD Seq. No. 0000) aligns the supporting document with the proposed changes listed in this review by adding the terms " buprenorphine-containing buccal films" and "Belbuca".

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission and find this change acceptable.

4 CONCLUSION AND RECOMMENDATION

DRISK recommends that Belbuca (buprenorphine hydrochloride buccal film) product-specific information should be included within the ER/LA Opioid Analgesic REMS Blueprint as appended to this review. The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on June 26, 2015.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK recommends that the redlined ER/LA Opioid Analgesic REMS for Belbuca (buprenorphine hydrochloride buccal film) (NDA 207932) appended to this review be shared with the Sponsor along with the following comments (*Section 6: Comments for the Applicant*). DRISK requests that the Sponsor respond to these comments within 5 days of receiving these comments to facilitate further review for this submission. The comments below are based on DRISK's preliminary review of the submission. In addition, the Sponsor should revise the REMS materials which are appended to this review.

6 COMMENTS FOR THE APPLICANT

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of ER/LA Opioid Analgesic REMS document, appended materials submitted on December 23, 2014. DRISK has the following comments, below, in response to the

Sponsor's proposal, including redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials.

1. Update the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* as described in the attached redlined document. Note this version is the most recently approved ER/LA Opioid Analgesic REMS approved on October 2, 2015 which includes Morphabond's[®] product specific information. This document must be aligned with any changes, if any, made to the Belbuca Prescribing Information.
2. The "Most Recent Modification" date on the REMS document must be changed to "XX/XXXX" as indicated in the redlined, attached REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.
3. Resubmission and Format Instructions:
 - a. Resubmission Requirements and Instructions: Submit the revised proposed ER/LA Opioid Analgesic REMS for Belbuca with appended materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.
 - b. Format Request: As noted previously, please submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. Please also submit for the Agency's review mocked up PDF versions of all the materials and webpages which show the intended layout and graphic design of each.

APPENDIX

Extended-Release and Long-Acting Opioid Analgesic REMS document and appended materials

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

/s/

DANNY S GONZALEZ
10/20/2015

KIMBERLY LEHRFELD
10/21/2015