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 ADDENDUM

Date:	April 22, 2016
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communications Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Director:	Cynthia LaCivita, Pharm. D. DRISK
Drug Name(s):	Xtampza ER (Oxycodone)
Therapeutic Class:	Opioid agonist
Dosage and Route:	9 mg, 13.5 mg, 27 mg, 36 mg extended-release oral capsules
Application Type/Number:	NDA 208090
Applicant/sponsor:	Collegium Pharmaceuticals, Inc.
OSE RCM #:	2014-2547; 2014-2549

*** 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 the Division of Risk Management's (DRISK's) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Xtampza ER (oxycodone) extended-release capsules (NDA 208090) submitted by Collegium Pharmaceuticals, Inc. (Collegium). Xtampza was tentatively approved on November 6, 2015. Collegium submitted a request for full approval as a Class I resubmission on February 26, 2016 and amended their application on March 3, 2016 and April 7, 2016.

If approved, Xtampza ER's risks of inappropriate prescribing, abuse andmisuse, addiction, unintentional overdose and death can be mitigated with labeling and a REMS. DRISK recommends Collegium be required to join the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA REMS).[1] DRISK agrees with the Sponsor's proposed REMS for Xtampza ER capsule and recommends full approval of the proposed REMS.

1 INTRODUCTION

The purpose of this review is to document Division of Risk Management's (DRISK's) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Xtampza ER (oxycodone) extended-release capsules (NDA 208090) submitted by Collegium Pharmaceuticals, Inc. (Collegium). Xtampza was tentatively approved[1] on November 6, 2015. Collegium submitted a request for full approval as a Class 1 resubmission on February 26, 2016 and amended their application on March 3, 2016 and April 7, 2016.

The NDA re-submission for Xtampza ER 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 April 20, 2016) with the addition of Xtampza product-specific information to the *FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics* (FDA Blueprint).

1.1 PRODUCT BACKGROUND

Xtampza ER (oxycodone), is a an abuse-deterrent (AD), extended-release (ER) formulation of oral oxycodone, with the proposed indication 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. Xtampza ER capsules abuse-deterrent properties are based on Collegium's proprietary abuse-deterrent technology. Xtampza ER capsules are comprised of an ER microsphere-in-capsule oxycodone formulation. The mechanism of action is consistent with the known profile of oxycodone. The formulation was designed to protect the active pharmaceutical ingredient from immediate release (IR) upon attempted manipulation of Xtampza ER.

OxyContin (oxycodone hydrochloride), the RLD, is an opioid agonist that is a part of the ER/LA opioid analgesic drug class. Oxycodone hydrochloride has been used clinically for more than 90 years and is widely recognized as an effective analgesic approved for use alone and in combination with other analgesic and/or anti-inflammatory drugs, including aspirin, ibuprofen, and acetaminophen. Oxycodone is a μ-opioid receptor

[1] Previously reviewed by DRISK. See the following DRISK review: Lehrfeld K. DRISK REMS Review for Xtampza ER, dated November 6, 2015.

agonist recognized as an effective and potent pain reliever with no ceiling dose for analgesic effectiveness. The precise mechanisms of pain control attributable to oxycodone are not known, although the compound is known to act as an agonist at mu (μ)-, kappa (κ)-, and delta (δ)-opioid receptors in the central nervous system (CNS). Oxycodone primarily affects μ -type opioid receptors. Specific central nervous system opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Collegium is seeking approval for Xtampza ER capsule strengths of 9 mg, 13.5 mg, 27 mg, and 36 mg. The Xtampza ER capsules are formulated to deliver the active ingredient over 12 hours. Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the RLD. At the time of submission, OxyContin tablets and Xtampza ER capsules have the same indication. Collegium conducted studies to evaluate the abuse deterrent properties of Xtampza ER (see Section 3.1.2). In vitro laboratory experiments have shown Xtampza ER to retain its ER properties when subjected to a wide variety of common methods of tampering and to resist methods of preparation for intravenous (IV) injection, nasal administration (insufflation), and inhalation (smoking). Additionally, pharmacokinetic (PK) studies have shown that tampering followed by oral or intranasal administration did not significantly increase peak oxycodone plasma exposure versus intact Xtampza ER capsules.

Due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting (ER/LA) opioid analgesics, ER/LA opioid analgesics are approved under a single shared system (SSS) REMS program.[2] The goal of the SSS REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

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

[2] 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

1.2 REGULATORY HISTORY

November 6, 2015: The Agency granted the Sponsor a tentative approval.

February 26, 2016: The Sponsor re-submitted their REMS submission to include a revised ER/LA Opioid REMS document, appended materials, and supporting document based on the most currently approved ER/LA REMS.

March 2, 2016: The Agency communicated with the Sponsor, via email, and recommended that they re-submit the most current and correct version of the ER/LA REMS which was originally shared with the RPC on February 23, 2016.

March 3, 2016: The Sponsor re-submitted their REMS submission to include a revised ER/LA Opioid REMS document, appended materials, and supporting document based on the most currently approved ER/LA REMS shared with the RPC on February 23, 2016.

April 5, 2016: The Agency communicated with the Sponsor, via email, and requested that they submit the version of the ER/LA Opioid REMS which is currently under review as a class-wide REMS modification and include Xtampza product-specific information within the *FDA Blueprint.*

April 7, 2016: The Sponsor submitted a revised version of the ER/LA Opioid REMS.

April 20, 2016: The Agency approved a modification to the ER/LA Opioid REMS that included additional administrative changes by the RPC.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 208090 for the proposed ER/LA Opioid REMS:

- Collegium Pharmaceuticals, Inc. Proposed REMS for Xtampza ER, NDA 208090, received February 26, 2016 (ORIG-1; eCTD Sequence No. 0052).
    - Amendment received March 3, 2016 (eCTD Sequence No. 0053).
    - Amendment received April 7, 2016 (eCTD Sequence No. 0056)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

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

- Collegium Pharmaceuticals, Inc. Draft Prescribing Information for Xtampza ER, received November 3, 2015 (ORIG-1; eCTD Seq. No. 0048).
    - Amendment received February 26, 2016 (eCTD Sequence No. 0052).
    - Amendment received April 12, 2016 (eCTD Sequence No. 0057).
- Gonzalez D. DRISK REMS Review for Xtampza ER, dated October 13, 2015.

- Extended Release and Long Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Lehrfeld K. DRISK REMS Review for Xtampza ER, dated October 30, 2015.
- Lehrfeld K. DRISK REMS Review for Xtampza ER, dated November 6, 2015.
- Gonzalez D. Risk Evaluation and Mitigation Strategy (REMS) Modification Review. February 24, 2016.
- Lee K. Office of Prescription Drug Promotion Review for Xtampza ER, dated April 8, 2016.
- Walker M. Patient Labeling Review for Xtampza ER, dated March 18, 2016.

3 RESULTS OF REVIEW OF THE PROPOSED REMS FOR XTAMPZA ER

The Sponsor's amendment proposes to incorporate Xtampza ER into the currently approved ER/LA Opioid REMS. This modification impacted the ER/LA Opioid REMS appended materials including the FDA Blueprint. DRISK reviewed Collegium's amended REMS proposal, received on April 7, 2016, in response to comments from the Agency provided on April 5, 2016 (see 1.2 Regulatory History).

3.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received April 7, 2016 has no additional changes beyond what has been approved by the Agency; therefore, DRISK finds it acceptable.

3.2 MEDICATION GUIDE

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Xtampza ER 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.[2,3]

3.3 REMS APPENDED MATERIALS

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

The Sponsor's proposal, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

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

The Office of Prescription Drug Promotion (OPDP) was consulted to review the *FDA Blueprint* related to Xtampza on July 28, 2015. Their review of Xtampza ER/LA REMS materials was entered into DAARTS on March 23, 2016. We did not ask them to review the other ER/LA REMS materials, as they were not changed with the addition of Xtampza

[2] Lee K. Office of Prescription Drug Promotion Review for Xtampza ER, dated April 8, 2016.
[3] Walker M. Patient Labeling Review for Xtampza ER, dated March 18, 2016.

to the ER/LA REMS.

DRISK notes that OPDP provided the following comments in their March 23, 2016 review of Xtampza, with which DRISK agrees:

OPDP does not object to the modifications made to the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*. We have no additional comments on these proposed REMS materials at this time.

The Sponsor's proposal for the *FDA Blueprint*, received April 7, 2016 includes the previously agreed upon Xtampza product specific language.[4] This is the only change to the *FDA Blueprint* beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

3.3.3 Prescriber Letters

The Sponsor's proposal for the Prescriber Letters, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

3.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

3.3.5 ER/LA Opioid Analgesic REMS website

The Sponsor's proposal for the website, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

3.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The Sponsor's proposal for the timetable, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

3.5 REMS SUPPORTING DOCUMENT

The Sponsor's proposed REMS supporting document, received April 7, 2016 has no additional changes beyond what has been approved by the Agency on April 20, 2016; therefore, DRISK finds it acceptable.

4 DISCUSSION AND CONCLUSION

A REMS for Xtampza ER 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 Xtampza ER. DRISK agrees with the Sponsor's proposal to amend their current REMS submission to align with the recently approved class-wide ER/LA Opioid REMS modification and include Xtampza

[4] Lehrfeld K. DRISK REMS Review for Xtampza ER, dated November 6, 2015.

ER within the ER/LA Opioid REMS.

The Sponsor submitted an amended REMS proposal for Xtampza ER on April 7, 2016 based on the Agency's comments (see Section 1.2). DRISK finds the amended ER/LA Opioid REMS (attached) acceptable; therefore, DRISK recommends approval of the REMS as appended to this review.

5 RECOMMENDATION

DRISK recommends approval of the ER/LA Opioid REMS for Xtampza ER (oxycodone capsules) (NDA 208090), received April 7, 2016 and as appended to this review.

6 ATTACHMENTS

Extended-Release and Long-Acting Opioid Analgesic REMS document and appended materials submitted by the Sponsor on April 7, 2016

46 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DANNY S GONZALEZ
04/21/2016

CYNTHIA L LACIVITA
04/21/2016
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 #:	208090
Product:	Xtampza ER (oxycodone extended-release capsules)
SPONSOR:	Collegium Pharmaceutical
FROM:	Judith A. Racoosin, MD, MPH
DATE:	November 6, 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, Xtampza ER will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
11/06/2015

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

FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	November 6, 2015
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communications Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Deputy Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Xtampza ER (Oxycodone)
Therapeutic Class:	Opioid agonist
Dosage and Route:	9 mg, 13.5 mg, 27 mg, 36 mg extended-release oral capsules
Application Type/Number:	NDA 208090
Applicant/sponsor:	Collegium Pharmaceuticals, Inc.
OSE RCM #:	2014-2547; 2014-2549

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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 Xtampza ER (oxycodone) extended-release capsules (NDA 208090) and evaluation of Collegium Pharmaceuticals, Inc. (Collegium) proposed REMS, received December 12, 2014 and amended on July 24, 2015, October 13, 2015, October 15, 2015, and on November 2, 2015. Collegium submitted an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the reference listed drug.

If approved, Xtampza ER's risks of abuse/misuse, addiction, overdose and death can be mitigated with labeling and a REMS. DRISK recommends Collegium be required to join the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA REMS) for Xtampza ER.[1] DRISK agrees with the Sponsor's proposed REMS for Xtampza ER capsule and recommends approval of the proposed REMS.

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 Xtampza ER (oxycodone) extended-release capsules (NDA 208090) and evaluation of Collegium's proposed REMS, received December 12, 2014 and amended on July 24, 2015, October 13, 2015, October 15, 2015, and on November 2, 2015. Collegium submitted an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the reference listed drug (RLD). The amended NDA submission for Xtampza ER 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 23, 2015).

1.1 PRODUCT BACKGROUND

Xtampza ER (oxycodone), is a an abuse-deterrent (AD), extended-release (ER) formulation of oral oxycodone, with the proposed indication 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. Xtampza ER capsules abuse-deterrent properties are based on Collegium's proprietary abuse-deterrent technology. Xtampza ER capsules are comprised of an ER microsphere-in-capsule oxycodone formulation. The mechanism of action are consistent with the known profile of oxycodone. The formulation was designed to protect the active pharmaceutical ingredient from immediate release (IR) upon attempted manipulation of Xtampza ER.

OxyContin (oxycodone hydrochloride), the RLD, is an opioid agonist that is a part of the ER/LA opioid analgesic drug class. Oxycodone hydrochloride has been used clinically for more than 90 years and is widely recognized as an effective analgesic approved for use alone and in combination with other analgesic and/or anti-inflammatory drugs, including aspirin, ibuprofen, and acetaminophen. Oxycodone is a μ-opioid receptor

[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.

agonist recognized as an effective and potent pain reliever with no ceiling dose for analgesic effectiveness.The precise mechanisms of pain control attributable to oxycodone are not known, although the compound is known to act as an agonist at mu (μ)-, kappa (κ)-, and delta (δ)-opioid receptors in the central nervous system (CNS). Oxycodone primarily affects μ -type opioid receptors. Specific central nervous system opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Collegium is seeking approval for Xtampza ER capsule strengths of 9 mg, 13.5 mg, 27 mg, and 36 mg. The Xtampza ER capsules are formulated to deliver the active ingredient over 12 hours. Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the RLD. At the time of submission, OxyContin tablets and Xtampza ER capsules have the same indication. Collegium conducted studies to evaluate the abuse deterrent properties of Xtampza ER (see Section 3.1.2) . In vitro laboratory experiments have shown Xtampza ER to retain its ER properties when subjected to a wide variety of common methods of tampering and to resist methods of preparation for intravenous (IV) injection, nasal administration (insufflation), and inhalation (smoking). Additionally, pharmacokinetic (PK) studies have shown that tampering followed by oral or intranasal administration did not significantly increase peak oxycodone plasma exposure versus intact Xtampza ER capsules.

Due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting (ER/LA) opioid analgesics, ER/LA opioid analgesics are approved under a single shared system (SSS) REMS program.[2] The goal of the SSS REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

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

[2] 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.

1.2 REGULATORY HISTORY

May 16, 2014: Collegium met with the Agency for a Pre-NDA meeting for IND 75786. At this meeting the Agency agreed with the overall bridging strategy. The Agency also confirmed Collegium's commitment to participate in the ER/LA Opioid REMS. The Agency confirmed that in order to satisfy REMS requirements the Sponsor must submit a proposed REMS with the NDA. The Agency also confirmed that the REMS Program Companies (RPC) will provide the most recently approved ER/LA Opioid REMS documents for the Sponsor to revise and submit with the NDA.

December 12, 2014: Collegium submitted a proposed REMS document, including appended materials, and REMS supporting document based their proposed label and the most recent version of the ER/RLA Opioid REMS (approved August 19, 2014).

June 26, 2015: The Agency approved a revised version of the ER/LA Opioid REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.

July 24, 2015: Collegium amended the submission to include Xtampza ER information in the June 26, 2015 version of the ER/LA Opioid REMS.

September 11, 2015: The Anesthetic and Analgesic Drug Products (AADP) Advisory Committee (AC) and Drug Safety and Risk Management (DSaRM) AC met to discuss the approvability of Xtampza ER due to potential food effects on safety and efficacy and potential safety risks related to abuse deterrent properties. The committee voted 23-0 for approval (See Section 3.3 for further details).

September 15, 2015: Office of Clinical Pharmacology determined that the NDA was acceptable from clinical pharmacology perspective based on totality of the data. [3]

October 2, 2015: The Agency approved Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA REMS.[4]

October 13, 2015: The Agency provided comments on labeling and the ER/LA REMS *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* to the Sponsor. The Sponsor amended the REMS submission to include the ER/LA REMS supporting document.

October 15, 2015: The Sponsor amended the submission to include a revised ER/LA Opioid REMS document, appended materials, and supporting document.

October 23, 2015: The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA Opioid REMS.[5]

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[3] Nallani S. Clinical Pharmacology Review Addendum for Xtampza ER (NDA 208090). September 24, 2015.

[4] Approval letter for Morphabond (morphine sulfate extended release tablet) NDA 206544, dated October 2, 2015.

[5] Approval letter for Belbuca (buprenorphine buccal film) NDA 207932, dated October 23, 2015.

October 30, 2015: The Agency provided comments to the Sponsor on the proposed REMS for Xtampza ER.[6]

November 2, 2015: The Sponsor amended the submission to include a revised ER/LA Opioid REMS document, appended materials, and supporting document based on the Agency's comments. This submission is the focus of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 208090 for the proposed ER/LA Opioid REMS:

- Collegium Pharmaceuticals, Inc. Proposed REMS for Xtampza ER, NDA 208090, received December 12, 2014 (ORIG-1; eCTD Sequence No. 0000).
    - Amendment received July 24, 2015 (eCTD Sequence No. 0024).
    - Amendment received October 13, 2015 (eCTD Sequence No. 0043).
    - Amendment received October 15, 2015 (eCTD Sequence No. 0045).
    - Amendment received November 2, 2015 (eCTD Sequence No. 0047).

2.2 OTHER MATERIALS INFORMING OUR REVIEW

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

- Collegium Pharmaceuticals, Inc. Draft Prescribing Information for Xtampza ER. received November 3, 2015 (ORIG-1; eCTD Seq. No. 0048).
- Galati S, Clinical Review for Xtampza ER, dated July 29, 2015.
- Pre-IND Meeting Minutes for Xtampza ER, dated March 8, 2007.
- End of Phase 2 Meeting Minutes for Xtampza ER, dated March 30, 2010.
- Tolliver J. Controlled Substance Staff Review for Xtampza ER, dated September 9, 2015.
- Nallani S. Clinical Pharmacology Review for Xtampza ER, dated September 8, 2015.
- Nallani S. Addendum to Clinical Pharmacology Review for Xtampza ER, dated September 24, 2015.
- Hertz S, Advisory Committee Background Materials for Xtampza ER, dated September 11, 2015.
- Walker M, Patient Labeling Review for Xtampza ER, dated October 5, 2015.
- Gonzalez D. DRISK REMS Review for Xtampza ER, dated October 13, 2015.

[6] Lehrfeld K. DRISK REMS Review for Xtampza ER, dated October 30, 2015.

- Extended Release and Long Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Lehrfeld K. DRISK REMS Review for Xtampza ER, dated October 30, 2015.
- Schlick J. Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review for Xtampza ER, dated September 10, 2015.

3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

To support the safety and efficacy of Xtampza ER, the Sponsor submitted the results of a pivotal Phase 3 trial, CP-OXYDET-08, using the to-be-marketed formulation, in conjunction with the Agency's previous findings of safety and efficacy for the RLD, OxyContin (NDA 22272), 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. CP-OXYDET-08 assessed the analgesic efficacy of the Xtampza ER formulation in the pain population. CP-OXYDET-08 was a multi-center, randomized, double-blind, placebo-controlled, safety, tolerability and efficacy study in both opioid-experienced and opioid-naïve subjets with moderate to severe chronic low back pain.

3.1 SUMMARY OF EFFICACY

3.1.1 Efficacy of Xtampza ER for the management of pain

The primary efficacy endpoint in study CP-OXYDET-08 was change in average pain intensity as measured by pain intensity-numerical rating scale (PI-NRS) scores from randomization baseline to Week 12 of the double-blind maintenance phase.The clinical reviewer[7] determined that the efficacy data reviewed in CP-OXYDET-8 supported the effectiveness of Xtampza ER based on the "statistical significance of the primary endpoint compared to placebo and the clinically meaningful benefit of this finding."

3.1.2 Efficacy of the abuse deterrent properties of Xtampza ER[8]

The abuse liability assessment for Xtampza ER relies on the applicable data from laboratory based in-vitro manipulation and extraction studies (Category 1), clinical PK studies (Category 2), and human abuse potential studies (Category 3) of Xtampza ER.

Category 1 - Laboratory Manipulation and Extraction Studies
Controlled Substance Staff (CSS) review of the in-vitro laboratory experiments concluded that the studies have shown Xtampza ER retains its ER properties when subjected to a wide variety of common methods of tampering. It also resists methods of preparation for intravenous (IV) injection, intranasal (IN) administration (insufflation), and inhalation (smoking). Based on the in-vitro manipulation and extraction studies, it was found that Xtampza ER capsule contents are difficult to crush. Xtampza ER results of in-vitro manipulation and extraction studies and the clinical PK studies suggest a possible resistance of Xtampza ER capsules to oral abuse following crushing or chewing. Xtampza ER capsule contents also resist dumping of oxycodone into aqueous solution

[7] Galati S, Clinical Review for Xtampza ER, dated July 29, 2015.

[8] Tolliver J. Controlled Substance Staff Review for Xtampza ER, September 9, 2015.

under varying conditions of temperature or agitation. However, the CSS reviewer also stated that it is not clear whether Xtampza ER 40 mg capsules provides a clinically meaningful deterrent effect to oral abuse. [9]

Category 2- Pharmacokinetic Studies

CSS review of four clinical PK studies (CP-OXYDET-19, -21, -24, and -25) concluded that the studies have shown that such tampering followed by oral or IN administration does not significantly increase peak oxycodone plasma exposure versus intact oral administration of Xtampza ER capsules (i.e., upon administration under fed conditions as intended for the treatment of pain). In addition, clinical abuse potential assessments conducted in 2 of these studies (CP-OXYDET-21 and -24) indicate that likeability of Xtampza ER is statistically significantly lower than IR oxycodone when these products are crushed and delivered crushed by the IN route or chewed by the oral route. Compared with other currently marketed oxycodone-containing products, this work indicates that the Xtampza ER formulation may result in reduced abuse by manipulation followed by oral ingestion, IN insufflation, or attempted IV injection. Results of the clinical PK study, CP-OXYDET-19, demonstrated IN Xtampza ER 40 mg crushed produced maximum oxycodone plasma level lower than that produced by oral intact Xtampza ER 40 mg or by 40 mg oxycodone powder intranasal. The clinical PK studies CP-OXYDET-19 and CP-OXYDET-25 demonstrated that oral crushed or chewed Xtampza ER is associated with significantly lower oxycodone Cmax than that from the positive comparator IR oxycodone hydrochloride solution.

Category 3 - Abuse Potential Studies

CSS concluded that in the human abuse potential study, CP-OXYDET-21, crushed Xtampza ER 40 mg, administered IN when compared to IN oxycodone 40 mg powder produced a lower peak plasma concentration of oxycodone (Cmax) and lower levels of drug liking and high as determined using the Drug Liking visual analog scale (VAS) and High VAS, respectively. However, in the human abuse potential study, CP-OXYDET-24, the results obtained regarding "subjective effects including drug liking were such as to question any clinical significance of the differences observed between chewed Xtampza ER and the IR oxycodonc HCl crushed oral solution."[9] This was the case even though these differences were statistically significantly different.

The CSS reviewer concluded that the results of the in-vitro manipulation and extraction studies, clinical PK studies, and human abuse potential studies studies suggest that Xtampza ER capsules are difficult to manipulate and may provide resistance to abuse by IN administration.

3.2 SUMMARY OF SAFETY

The clinical data supporting the safety claim for Xtampza ER is based on 1 Phase 3 study (CP-OXYDET-08). According to the Sponsor, the results of the evaluation of safety data from this study demonstrate that the safety profile for Xtampza ER is consistent with the known safety profile for oxycodone and the medical status of the subject population –

[9] Tolliver J. Controlled Substance Staff Review for Xtampza ER, September 9, 2015.

patients with chronic pain. The Sponsor also concluded that no new safety signals were detected with respect to adverse events (AEs), clinical laboratory changes, and other safety measures when compared with safety findings for OxyContin.

A total of 366 subjects reported 845 treatment-related AEs in the maintenance phase of the study. The Sponsor reported that the most frequently reported preferred terms were nausea (15.1%), constipation (12.8%), headache (9.5%), somnolence (8.6%), pruritus (7.0%), vomiting (5.4%), and dizziness (5.3%), which are expected AEs for this product. The incidences of serious adverse events (SAE) and study drug-associated SAEs/severe AEs were 1.1% (8 subjects) and 0.3% (2 subjects).

One death was reported during the clinical study; however, it was not considered related to Xtampza ER per the Investigator's assessment. Eight subjects during the initial titration phase and 4 subjects (2 Xtampza ER subjects; 2 placebo subjects) during the double-blind maintenance phase experienced serious TEAEs, including the aforementioned death.

The clinical reviewer concluded that "no new safety signal was identified during the review of this application."[10] In addition, DAAAP recommended that if approved, this product will be required to become a part of the ER/LA Opioid Analgesics REMS.[11]

Food effect on Pharmacokinetics The Sponsor evaluated the food-effect in several studies including CP-OXYDET-08. Subjects took their study drug with food >98% of the time during clinical trials. Moreover, the few subjects in Study CP-OXYDET-08 who took their study drug without food (0.2%) did not have any qualifying events (study drug-associated SAEs/severe AEs) based on the adjudication results of the Sponsor's expert committee. In addition, key results of the analysis attempting to link AEs to the meal data captured in the electronic diary on the days of interest—the day prior to and day of AE onset – showed that even under the extreme meal pattern of no meal followed by a heavy meal, which occurred in ≤0.1% of the time across the study, there was a low AE incidence of ≤ 0.2% in the titration phase and 0% in the double-blind maintenance hase. In summary, the Sponsor concluded that there was no association between food and exacerbation of AEs, and more generally, no anticipated safety concern with subjects not taking Xtampza ER with food as directed. In addition, during Study CP-OXYDET-08, a food effect protocol assessing pharmacokinetic safety was implemented. Overall, there were 3 qualifying events in the study, but no causal relationship among study drug, meal (size), and the SAE/severe AE were detected by the Sponsor. The Sponsor concluded that the food effect identified above in CP-OXYDET-18 does not appear to be clinically meaningful under a multiple-dose regimen and under the naturalistic conditions of a large, randomized, double-blind clinical study in the intended patient population.

However, the clinical reviewer disagreed with the Sponsor's conclusion and recommended a complete response for Xtampza ER (9 mg, 13.5 mg, 27 mg, and 36 mg capsules) based on the data provided by the Sponsor. The clinical reviewer[12] summarized ~~the risk/benefit of Xtampza ER~~ as follows:

[10] Galati S, Clinical Review for Xtampza ER, dated July 29, 2015.

[11] Hertz S, Advisory Committee Background Materials for Xtampza ER, September 11, 2015.

Overall, the risk-benefit profile of Xtampza ER in this patient population is questionable. The real-world scenario of patients taking a high-fat-high-calorie meal on a consistent basis is not realistic, especially when other opioid products do not have this restriction. A major concern would be the variably serum levels leading to inconsistent dosing in an individual. If a patient does not achieve the desired analgesic effect (due to not taking with food) and then takes another dose with food the serum levels may rapidly rise and lead to serious complications. Therefore, I recommend a Complete Response. This review is prior to the upcoming Advisory Committee scheduled September 11, 2015. The key issues, most notably the food effect and potential clinical impact, will be further discussed at that time.

The clinical pharmacology reviewer also concluded that there was the potential for a food effect with the use of Xtampza ER.[13] The clinical pharmacology reviewer concluded that there was a food effect when compared to the RLD, OxyContin, and stated:

Xtampza relative bioavailability is lower compared to OxyContin under fasting condition and taking Xtampza with food increases bioavailability.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer was concerned that:

...the currently proposed packaging, labels, and labeling do not appropriately mitigate the risk for administration errors due to the food effect.[14]

DMEPA recommended revisions to the packaging, labels, and labeling to better communicate the food effect. DMEPA recommended the following language be included in the labeling:

(b) (4)

The clinical and clinical pharmacology review team saught input from the AADP and DSaRM Advisory Committee about the food effect as discussed belowan (see section 3.3).

3.3 SUMMARY OF ADVISORY COMMITTEE MEETING

On September 11, 2015,the AADP AC and DSaRM AC for Xtampza ER [15,16] met to discuss the approvability to Xtampza ER due to potential food effects on safety and efficacy and potential safety risks related to abuse deterrent propoerties.[17] The PK data

[12] Galati S. Clinical Review for Xtampza ER, dated July 29, 2015.

[13] Nallani S. Clinical Pharmacology Review for Xtampza ER, dated September 8, 2015.

[14] Schlick J. Label and Labeling Review for Xtampza ER, dated September 10, 2015

[15] Hertz S, Advisory Committee Background Materials for Xtampza ER, September 11, 2015.

[16] FDA Advisory Committee for Xtampza ER (NDA 208090). Scheduled for September 11, 2015.

[17] Galati S, Clinical Review for Xtampza ER, dated July 29, 2015.

provided by the Sponsor demonstrated that, in order to deliver the intended amount of oxycodone, the drug product must be taken with food. The AC was also asked to consider the potential safety risks given the potential fluctuations in oxycodone levels that may occur if the product is not taken consistently with the same amount of food. The AC recommended 23-0 for approval for many reasons, including that the Sponsor evaluated the food-effect on efficacy and safety in a Phase 3 clinical trial recommended by the Agency and no evidence concerning meal type had an impact on the safety and efficacy profile. In addition, the AC noted that the chronic indication for this product will help to mitigate the risk of fluctuating oxycodone concentrations because the patients should have a steady-state serum drug concentration due to the chronic use. The AC made a recommendation to include language in the label to take Xtampza ER with food.

In addition, the AC was asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The AC thought that the product provided an incremental improvement in abuse-deterrent opioid formulation. At the conclusion of the AC, the committee voted unanimously supporting approval of Xtampza ER (23 for approval : 0 against approval).

Post-AC

On September 15, 2015, the Office of Clinical Pharmacology met to discuss the outcomes of the AC and determined that the NDA was acceptable based on totality of the data. The Office of Clinical Pharmacology agreed that Xtampza ER should be labeled as taken with food; however, the amount and type of the food does not need to be specified in the label. [18]

4 RATIONALE FOR A REMS FOR XTAMPZA ER

DRISK agrees with the Sponsor and DAAAP 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 Xtampza ER. 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 IR 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 ER features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an IR manner, potentially resulting in overdose or death. Therefore, the ER/LA Opioid Analgesic REMS was developed and approved to mitigate these risks.

Xtampza ER includes an abuse-deterrent formulation that may mitigate the risk of intravenous or IN abuse. In addition, tablets retained the ER properties upon crushing and extraction. Also, Xtampza ER capsules, compared to OxyContin, are difficult to manipulate and may provide resistance to abuse by IN administration. , Xtampza ER

[18] Nallani S. Clinical Pharmacology Review Addendum for Xtampza ER (NDA 208090). September 24, 2015.

contains oxycodone in doses which could potentially result in overdose or death due to the high amounts of oxycodone. Therefore the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse remain despite the abuse-deterrent formulation in this opioid product.

If approved, Xtampza ER'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. As an ER 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. Thus, it is appropriate for it to join the single, shared system ER/LA Opioid REMS.

5 RESULTS OF REVIEW OF THE PROPOSED REMS FOR XTAMPZA ER

The Sponsor proposed to incorporate Xtampza ER into the approved ER/LA Opioid REMS. This modification impacted the ER/LA Opioid REMS appended materials including the FDA Blueprint. DRISK reviewed Collegium's proposed REMS, received on November 2, 2015, in response to comments from the Agency provided on October 30, 2015.[19]

5.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received November 2, 2015 has no additional changes; therefore, DRISK finds it acceptable.

5.1.1 Medication Guide

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Xtampza ER 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.[20]

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 November 2, 2015 has no additional changes; therefore, DRISK finds it acceptable.

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

The Sponsor proposed to include Xtampza ER product-specific language in the FDA Blueprint. DRISK and DAAAP find the proposed changes, received November 2, 2015, that incorporate the Agency's feedback acceptable.

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[19] Lehrfeld K. DRISK REMS Review for Xtampza ER, dated October 30, 2015

[20] Walker M, Patient Labeling Review for Xtampza ER, dated October 5, 2015.

5.1.2.3 Prescriber Letters

The Sponsor's proposal, received November 2, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.1.2.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, received November 2, 2015 has no additional changes; therefore, DRISK finds them acceptable.

5.1.2.5 ER/LA Opioid Analgesic REMS website

The Sponsor's proposed REMS website, received November 2, 2015 has no additional changes; therefore, DRISK finds it acceptable.

5.1.3 Timetable for Submission of Assessments

The Sponsor's proposal, received November 2, 2015, has no additional changes; therefore, DRISK finds it acceptable.

5.2 REMS SUPPORTING DOCUMENT

The Sponsor's proposed REMS supporting document, received November 2, 2015 has no additional changes; therefore, DRISK finds it acceptable.

6 DISCUSSION AND CONCLUSION

A REMS for Xtampza ER 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 Xtampza ER. DRISK agrees with the Sponsor's proposal to include Xtampza ER within the ER/LA Opioid REMS.

The Sponsor submitted a proposed REMS for Xtampza ER on November 2, 2015 based on the Agency's comments[21]. DRISK finds the proposed ER/LA Opioid REMS (attached) acceptable; therefore, DRISK recommends a approval of the REMS as appended to this review.

7 RECOMMENDATION

DRISK recommends approval of the ER/LA Opioid REMS for Xtampza ER (oxycodone capsules) (NDA 208090), received November 2, 2015 and as appended to this review.

Once the application is ready for full approval, DRISK should be sent a new consult to review the REMS for Xtampza ER to ensure no additional changes are necessary.

8 ATTACHMENTS

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

[21] Lehrfeld K. DRISK REMS Review for Xtampza ER, dated October 30, 2015.

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

/s/

KIMBERLY LEHRFELD
11/06/2015

REEMA J MEHTA
11/06/2015
I concur.

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 30, 2015
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communication Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Acting Deputy Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Xtampza (Oxycodone)
Therapeutic Class:	Opioid agonist
Dosage and Route:	9 mg, 13.5 mg, 27 mg, 36 mg extended-release oral capsules
Application Type/Number:	NDA 208090
Submission Number:	ORIG-1
Applicant/sponsor:	Collegium Pharmaceuticals, Inc.
OSE RCM #:	2014-2547; 2014-2549

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

CONTENTS

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of Collegium Pharmaceuticals, Inc. (Collegium) REMS submission, received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and amended on October 15, 2015 (ORIG-1; eCTD Seq. No. 0045). Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the reference listed drug (RLD). The Sponsor is currently an observer company in the REMS Program Companies (RPC) and must join the RPC prior to marketing their product under the single, shared system ER/LA Opioid Analgesic REMS. On October 15, 2015, Collegium re-submitted a proposal which included Xtampza 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

Xtampza (oxycodone), is a an abuse-deterrent (AD), extended-release (ER) formulation of oral oxycodone, with the proposed indication 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. Xtampza capsules abuse-deterrent properties are based on Collegium's proprietary abuse-deterrent technology. Xtampza capsules are comprised of an ER microsphere-in-capsule oxycodone formulation. The formulation was designed to protect the active pharmaceutical ingredient from immediate release upon attempted manipulation of Xtampza.

OxyContin (oxycodone hydrochloride), the RLD, is an opioid agonist that is a part of the ER/LA opioid analgesic drug class. Oxycodone hydrochloride has been used clinically for more than 90 years and is widely recognized as an effective analgesic approved for use alone and in combination with other analgesic and/or anti-inflammatory drugs, including aspirin, ibuprofen, and acetaminophen.Oxycodone hydrochloride is a commercially available, semi-synthetic opioid with opioid receptor agonist properties. Oxycodone is a μ-opioid receptor agonist recognized as an effective and potent pain reliever with no ceiling dose for analgesic effectiveness.The precise mechanisms of pain control attributable to oxycodone are not known, although the compound is known to act as an agonist at mu (μ)-, kappa (κ)-, and delta (δ)-opioid receptors in the central nervous system (CNS). Oxycodone primarily affects μ -type opioid receptors. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Collegium is seeking approval for Xtampza capsule strengths of 9 mg, 13.5 mg, 27 mg, and 36 mg. The ER Xtampza capsules are formulated to deliver the active ingredient (b) (4) Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the RLD. At the time of submission, OxyContin tablets approved indication and Xtampza capsules proposed indication were identical. Collegium has conducted one clinical study in the target pain population and is also relying on FDA's previous finding of safety and effectiveness for OxyContin, as summarized in the approved prescribing information (PI) (OxyContin PI, October 2014).

Collegium has conducted clinical comparative bioavailability (BA) bridging studies for FDA's finding of safety and efficacy for OxyContin. Collegium has also conducted extensive Category 1 laboratory manipulation and extraction studies and a combination Category 2 pharmacokinetics (PK) study/Category 3 human abuse-potential study. In vitro laboratory experiments have shown Xtampza to retain its ER properties when subjected to a wide variety of common methods of tampering and to resist methods of preparation for intravenous (IV) injection, nasal administration (insufflation), and inhalation (smoking). Additionally, PK studies have shown that tampering followed by oral or intranasal administration did not significantly increase peak oxycodone plasma exposure versus intact Xtampza capsules. While the formulation is abuse resistant, abuse of Xtampza is still possible. Thus, the risk of abuse is not completely eliminated.

Thus, like other extended-release opioid products, Xtampza poses a risk of abuse/misuse, addiction, overdose and death. Due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting (ER/LA) opioid analgesics, ER/LA opioid analgesics are approved under a single shared system (SSS) REMS program. The proposed indication for Xtampza is consistent with the products in the single shared system (SSS) REMS for extended-release/long-acting (ER/LA) opioid analgesic drug products. If approved Xtampza will become a part of the SSS ER/LA opioid REMS.[1]

On July 9, 2012, the FDA approved a SSS REMS for ER/LA opioid analgesic drug products.[1] The goal of the SSS REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

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] 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.

1.2 REGULATORY HISTORY

April 16, 2014: Collegium met with the Agency for a Pre-NDA meeting for IND 75786. At this meeting the Agency agreed with the overall bridging strategy. The Agency also Collegium's commitment to participate in the ER/LA REMS program. The Agency confirmed that in order to satisfy REMS requirements the Sponsor must submit a proposed REMS with this NDA. The Agency also confirmed that the REMS Program Companies (RPC) will provide the most recently approved ER/LA REMS documents for the Sponsor to revise and submit with the NDA.

December 12, 2014: Collegium submitted (ORIG-1; eCTD Seq. No. 0000) REMS documents and materials based their proposed label and the most recent version of the ER/RLA Opioid REMS (August 19, 2014).

July 24, 2015: Collegium submitted (ORIG-1; eCTD Seq. No. 0024) an updated REMS based on the recently approved ER/LA Opioid REMS approved on June 3, 2015.

September 11, 2015: The Agency's Advisory Committee (AC) met with Collegium to discuss inconsistent pharmacokinetic (PK) data. Xtampza ER has potential safety risks and potential effects on efficacy associated with the extent of the food effect, as well as potential fluctuations in plasma oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the AC was asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse, and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The AC voted unanimously (23, 0) that Xtampza ER should be approved for marketing in the United States.

October 13, 2015: The Agency provided comments to the Sponsor[2] on their July 24, 2015 submission of the ER/LA Opioid REMS. The Agency returned comments were based on the labeling and the ER/LA REMS' *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* to the Sponsor for review.

October 13, 2015: The Sponsor submitted the ER/LA REMS supporting document (ORIG-1; eCTD Seq. No. 0043).

October 15, 2015: Collegium submitted (ORIG-1; eCTD Seq. No. 0045) an updated REMS based on the recently approved ER/LA Opioid REMS approved on June 3, 2015 and feedback provided by the Agency. These documents are the focus of this review.

October 23, 2015: The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA REMS. [3]

[2] Gonzalez D. REMS Review for Xtampza ER, dated October 13, 2015.

[3] Approval letter for Belbuca (buprenorphine buccal film) NDA 207932, dated October 23, 2015.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 206627 for the proposed ER/LA Opioid Analgesics REMS:

- Collegium Pharmaceuticals, Inc. Amendment to New Drug Application for NDA 208090 (ORIG-1; eCTD Sequence No. 0024). Submitted July 24, 2015.
    - Amendment received October 13, 2015 (ORIG-1; eCTD Seq. No. 0043)
    - Amendment received October 15, 2015 (ORIG-1; eCTD Seq. No. 0045).

2.2 MATERIALS INFORMING OUR REVIEW

- Collegium Pharmaceuticals, Inc. Draft Prescribing Information (PI) for Xtampza. Submitted April 24, 2015 (ORIG-1; eCTD Seq. No. 0017)
    - FDA revised, draft PI for Xtampza, emailed to the Sponsor the week of October 13, 2015.
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on June 26, 2015.
- Galati S, Clinical Review for Xtampza, July 29, 2015.
- Tolliver J. Controlled Substance Staff Review for Xtampza, September 9, 2015.
- Gonzalez D. REMS Review for Xtampza ER, dated October 13, 2015.
- Walker M. Patient Labeling Review for Xtampza ER, dated October 5, 2015.

3 DRISKS'S EVALUATION OF THE PROPOSED REMS

3.1 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 to be acceptable.[4]

3.2 REMS DOCUMENT

The Sponsor's proposed REMS document, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), has no additional changes; therefore, DRISK finds them acceptable.

3.3 APPENDED MATERIALS

[4] Walker M. Patient Labeling Review for Xtampza ER, dated October 5, 2015.

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

The Sponsor's proposal, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), 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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), incorporates the Xtampza product-specific information; however, the Sponsor included the following additional edits.

- Addition of the term [redacted] (b) (4)
- Addition of the following language describing oxycodone equivalent strengths: [redacted] (b) (4) *)*
- Changes to the maximum daily dose [redacted] (b) (4) to *288 mg (8 * 36 mg capsules)*
- Removal of the following statement: [redacted] (b) (4)
- Removal of [redacted] (b) (4) instructions to avoid redundancy.
- Aligning the following renal impairment language with the current labeling: [redacted] (b) (4) *follow a conservative approach to dose initiation and adjust according to the clinical situation.*

DRISK Comments: DRISK and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) have reviewed the submission, agree with the Sponsor's proposed edits and has the following additional clarifying edit to the Xtampza Product Specific information in the Blueprint(see below).

[redacted] (b) (4)

Finally, on October 23, 2015, a new ER/LA product, Belbuca buccal film, was approved with a revised ER/LA REMS. These revisions will also need to be incorporated in the Sponsor's next submission and are included in the redlined, attached materials.

3.3.3 Prescriber Letters

The Sponsor's proposal, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), has no additional changes.

Reviewer Comment: The addition of Belbuca to the ER/LA REMS required the following revision to these letters.

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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), 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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), has no additional changes.

Reviewer Comment: The addition of Belbuca to the ER/LA REMS required the following revision to the Important Safety Information on the ER/LA REMS website.

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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted October 15, 2015 (ORIG-1; eCTD Sequence No. 0045), has no additional changes; therefore, DRISK finds them acceptable.

4 CONCLUSION AND RECOMMENDATION

DRISK recommends that Xtampza ER (oxycodone) capsules product-specific information should be included within the ER/LA Opioid Analgesic REMS Blueprint as appended to this review. The product specific information for Belbuca, which was approved on October 23, 2015 as part of the ER/LA REMS, must also be incorporated into the ERLA REMS materials (Blueprint, Prescriber Letters, and Website) 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 Xtampza ER (oxycodone) capsule (NDA 208090) 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 by November 2, 2015 to facilitate further review for this submission.

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 October 15, 2015. 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. Please note the additional track changes and comments in the attached *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.
2. NOTE: On October 23, 2015, a new ER/LA product, Belbuca buccal film, was approved by the Agency with a revised ER/LA REMS. The attached ER/LA REMS materials includes Belbuca's product specific information in the Blueprint, Prescriber Letters and Website where noted. If approved, Xtampza's REMS must include Belbuca's product specific information.
3. The "Most Recent Modification" date on the REMS document must be "XX/XXXX" as indicated in the redlined, attached PDF 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.
4. Resubmission and Format Instructions:
    a. Resubmission Requirements and Instructions: Submit the revised proposed ER/LA Opioid Analgesic REMS for Xtampza 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.

Also submit the attached, PDF document which includes the ER/LA REMS and all appended materials.

APPENDIX

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

45 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KIMBERLY LEHRFELD
10/30/2015

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 13, 2015
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communication Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Acting Deputy Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Xtampza (Oxycodone)
Therapeutic Class:	Opioid agonist
Dosage and Route:	9 mg, 13.5 mg, 27 mg, 36 mg extended-release oral capsules
Application Type/Number:	NDA 208090
Submission Number:	ORIG-1
Applicant/sponsor:	Collegium Pharmaceuticals, Inc.
OSE RCM #:	2014-2547; 2014-2549

CONTENTS

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of Collegium Pharmaceuticals, Inc. (Collegium) REMS submission, received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and amended on July 24, 2015 (ORIG-1; eCTD Seq. No. 0024). Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the reference listed drug (RLD). The Sponsor is currently an observer company in the REMS Program Companies (RPC) and must join the RPC prior to marketing their product under the single, shared system ER/LA Opioid Analgesic REMS. On July 24, 2015, Collegium submitted a proposal which included Xtampza (referred to as *Oxycodone DETERx* in the submission) 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

Xtampza (oxycodone), is a an abuse-deterrent (AD), extended-release (ER) formulation of oral oxycodone, with the proposed indication 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. Xtampza capsules abuse-deterrent properties are based on Collegium's proprietary abuse-deterrent technology. Xtampza capsules are comprised of an ER microsphere-in-capsule oxycodone formulation. The formulation was designed to protect the active pharmaceutical ingredient from immediate release upon attempted manipulation of Xtampza.

OxyContin (oxycodone hydrochloride), the RLD, is an opioid agonist that is a part of the ER/LA opioid analgesic drug class. Oxycodone hydrochloride has been used clinically for more than 90 years and is widely recognized as an effective analgesic approved for use alone and in combination with other analgesic and/or anti-inflammatory drugs, including aspirin, ibuprofen, and acetaminophen.Oxycodone hydrochloride is a commercially available, semi-synthetic opioid with opioid receptor agonist properties. Oxycodone is a μ-opioid receptor agonist recognized as an effective and potent pain reliever with no ceiling dose for analgesic effectiveness.The precise mechanisms of pain control attributable to oxycodone are not known, although the compound is known to act as an agonist at mu (μ)-, kappa (κ)-, and delta (δ)-opioid receptors in the central nervous system (CNS). Oxycodone primarily affects μ -type opioid receptors. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Collegium is seeking approval for Xtampza capsule strengths of 9 mg, 13.5 mg, 27 mg, and 36 mg. The ER Xtampza capsules are formulated to deliver the active ingredient (b) (4) Collegium is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's OxyContin (NDA 22272) as the RLD. At the time of submission, OxyContin tablets approved indication and Xtampza capsules proposed indication were identical. Collegium has conducted one clinical study in the target pain population and is also relying on FDA's previous finding of safety and effectiveness for OxyContin, as

summarized in the approved prescribing information (PI) (OxyContin PI, October 2014). Collegium has conducted clinical comparative bioavailability (BA) bridging studies for FDA's finding of safety and efficacy for OxyContin. Collegium has also conducted extensive Category 1 laboratory manipulation and extraction studies and a combination Category 2 pharmacokinetics (PK) study/Category 3 human abuse-potential study. In vitro laboratory experiments have shown Xtampza to retain its ER properties when subjected to a wide variety of common methods of tampering and to resist methods of preparation for intravenous (IV) injection, nasal administration (insufflation), and inhalation (smoking). Additionally, PK studies have shown that tampering followed by oral or intranasal administration did not significantly increase peak oxycodone plasma exposure versus intact Xtampza capsules. While the formulation is abuse resistant, abuse of Xtampza is still possible. Thus, the risk of abuse is not completely eliminated.

Thus, like other extended-release opioid products, Xtampza poses a risk of abuse/misuse, addiction, overdose and death. Due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting (ER/LA) opioid analgesics, ER/LA opioid analgesics are approved under a single shared system (SSS) REMS program. The proposed indication for Xtampza is consistent with the products in the single shared system (SSS) REMS for extended-release/long-acting (ER/LA) opioid analgesic drug products. If approved Xtampza will become a part of the SSS ER/LA opioid REMS.[1]

On July 9, 2012, the FDA approved a SSS REMS for ER/LA opioid analgesic drug products.[1] The goal of the SSS REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

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] 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.

1.2 REGULATORY HISTORY

April 16, 2014: Collegium met with the Agency for a Pre-NDA meeting for IND 75786. At this meeting the Agency agreed with the overall bridging strategy. The Agency also Collegium's commitment to participate in the ER/LA REMS program. The Agency confirmed that in order to satisfy REMS requirements the Sponsor must submit a proposed REMS with this NDA. The Agency also confirmed that the REMS Program Companies (RPC) will provide the most recently approved ER/LA REMS documents for the Sponsor to revise and submit with the NDA.

December 12, 2014: Collegium submitted (ORIG-1; eCTD Seq. No. 0000) REMS documents and materials based their proposed label and the most recent version of the ER/RLA Opioid REMS (August 19, 2014).

July 24, 2015: Collegium submitted (ORIG-1; eCTD Seq. No. 0024) an updated REMS based on the recently approved ER/LA Opioid Analgesics REMS approved on June 3, 2015. These documents are the focus of this review.

September 11, 2015: The Agency's Advisory Committee (AC) met with Collegium to discuss inconsistent pharmacokinetic (PK) data. Xtampza ER has potential safety risks and potential effects on efficacy associated with the extent of the food effect, as well as potential fluctuations in plasma oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the AC was asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse, and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The AC voted unanimously (23, 0) that Xtampza ER should be approved for marketing in the United States.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 206627 for the proposed ER/LA Opioid Analgesics REMS:

- Collegium Pharmaceuticals, Inc. Amendment to New Drug Application for NDA 208090 (ORIG-1; eCTD Sequence No. 0024). Submitted July 24, 2015.

2.2 MATERIALS INFORMING OUR REVIEW

- Collegium Pharmaceuticals, Inc. Draft Prescribing Information (PI) for Xtampza. Submitted April 24, 2015 (ORIG-1; eCTD Seq. No. 0017)
    - FDA revised, draft PI for Xtampza, which will be emailed to the Sponsor the week of October 13, 2015.
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on June 26, 2015.
- Galati S, Clinical Review for Xtampza, July 29, 2015.

- Tolliver J. Controlled Substance Staff Review for Xtampza, September 9, 2015.

3 DRISKS'S EVALUATION OF THE PROPOSED REMS

3.1 MEDICATION GUIDE

The OPDP/Patient Labeling Review Team's (LRT) review is ongoing. The OPDP/LRT is reviewing the Sponsor's proposed Xtampza Medication Guide (MG) under separate cover and will communicate their recommendations to the Sponsor once their review is complete.

3.2 REMS DOCUMENT

The Sponsor's proposed REMS document, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), has no additional changes; therefore, DRISK finds them acceptable.

3.3 APPENDED MATERIALS

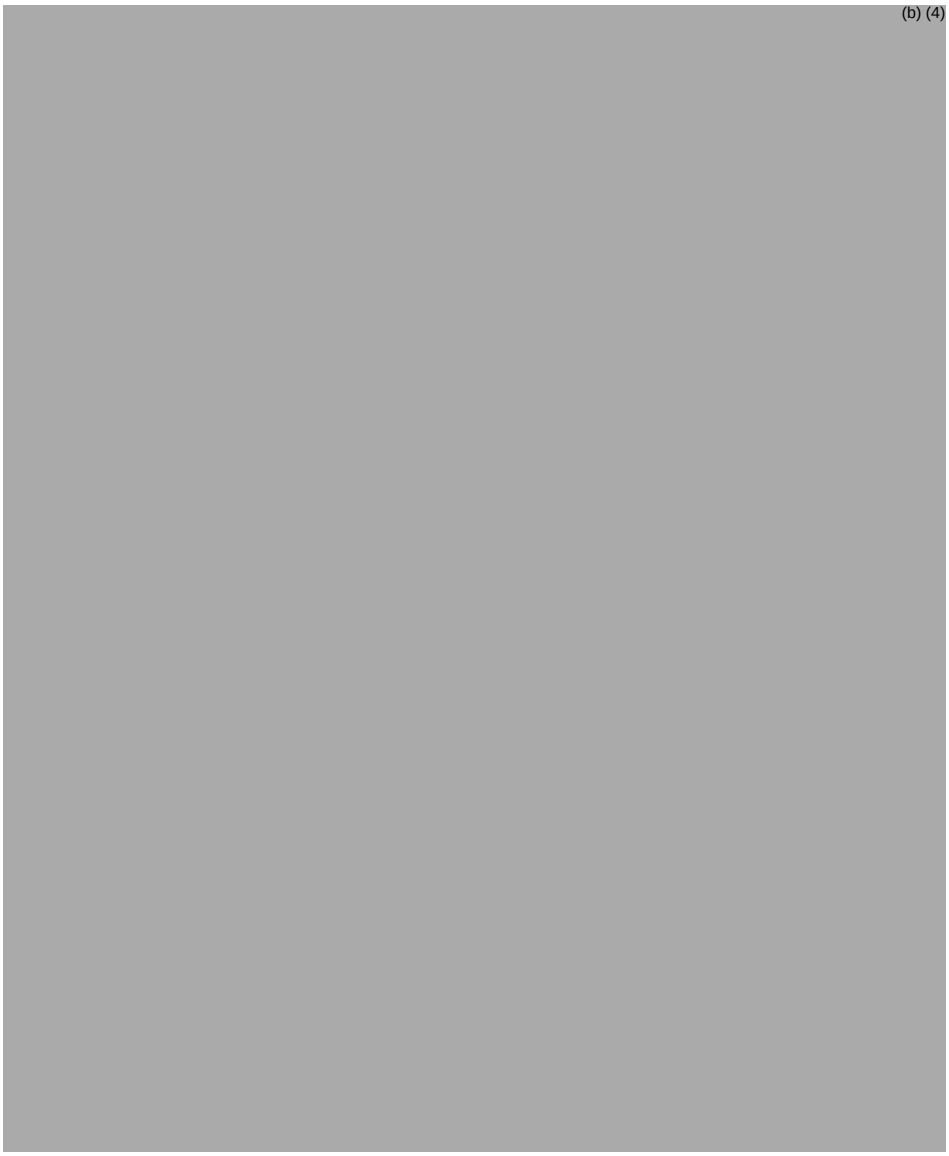
3.3.1 Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics

The Sponsor's proposal, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), 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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), incorporates the Xtampza product-specific information; however, the Sponsor refers to the product by a different name (Oxycodone DETERx). DRISK and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) have reviewed the submission (see below) and summarized the comments below. The Agency's agreed upon document is appended to this review.

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission and recommend the changes summarized below.



3.3.3 Prescriber Letters

The Sponsor's proposal, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), has no additional changes; therefore, DRISK finds them acceptable.

3.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, originally received December 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), 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 12, 2014 (ORIG-1; eCTD Seq. No. 0000) and re-submitted July 24, 2015 (ORIG-1; eCTD Sequence No. 0024), has no additional changes; therefore, DRISK finds them acceptable.

3.4 REMS SUPPORTING DOCUMENT

The Sponsor did not submit a REMS supporting document.

DRISK Comments:The Sponsor must submit the ER/LA REMS REMS Supporting Document for review. The REMS submission is not complete and the REMS cannot be approved without this component. DRISK will request submission and instruct the Sponsor to obtain this document from the RPC.

4 CONCLUSION AND RECOMMENDATION

DRISK recommends that Xtampza (oxycodone) capsules 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 Xtampza (oxycodone) capsule (NDA 208090) 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 July 24, 2015. 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. The ER/LA Opioid Analgesic REMS Supporting document must be submitted to your application in order to take action on this NDA. The ER/LA Opioid Analgesic REMS Supporting document can be obtained from the ER/LA Opioid Analgesic REMS Program Companies (RPC).
2. Update the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* as described in the attached redlined document. Note this verison 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 Xtampza Prescribing Information.
3. 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.

4. Resubmission and Format Instructions:
    a. Resubmission Requirements and Instructions: Submit the revised proposed ER/LA Opioid Analgesic REMS for Xtampza 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 Anagesic REMS document and appended materials

46 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DANNY S GONZALEZ
10/13/2015

KIMBERLY LEHRFELD
10/13/2015