# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207621Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

# Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

| | |
|---|---|
| **NDA #:** | 207621 |
| **Product:** | Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules |
| **SPONSOR:** | Pfizer, Inc. |
| **FROM:** | Judith A. Racoosin, MD, MPH |
| **DATE:** | See electronic signature |

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 would be 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, Troxyca ER will be joining this single shared system REMS.

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JUDITH A RACOOSIN
08/18/2016

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

# FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

| | |
|---|---|
| Date: | July 8, 2016 |
| Reviewers: | Kimberly Lehrfeld, Pharm. D.<br>Team Leader<br>Division of Risk Management (DRISK)<br><br>Joan Blair, R.N., M.P.H.<br>Health Communication Analyst<br>DRISK |
| Team Leader: | Kimberly Lehrfeld, Pharm. D.<br>DRISK |
| Director: | Cynthia LaCivita, Pharm. D.<br>DRISK |
| Drug Name(s): | Troxyca ER (oxycodone hydrochloride /naltrexone hydrochloride) |
| Therapeutic Class: | Opioid agonist/opioid antagonist |
| Dosage and Route: | 10 mg/1.2 mg , 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8mg, 60 mg/7.2 mg, and 80 mg/9.6 (oxycodone/naltrexone) abuse-deterrent, extended-release oral capsule |
| Application Type/Number: | NDA 207621 |
| Submission Number: | ORIG-1 |
| Applicant/sponsor: | Pfizer, Inc. |
| OSE RCM #: | 2014-2592; 2014-2593 |

*** 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 Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] extended-release (ER) capsules (NDA 207621) and evaluation of Pfizer, Inc. (Pfizer) proposed REMS, received December 19, 2014 and amended on April 1, 2015, July 24, 2015, December 11, 2015, January 8, 2016, May 25, 2016, and June 6, 2016. Pfizer submitted NDA 207621 on December 19, 2014 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the reference listed drugs.

If approved, Troxyca ER's risks of abuse/misuse, addiction, overdose and death will be mitigated with labeling and a REMS. Pfizer is currently a member of the the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS.[1] DRISK agrees with the Sponsor's proposed REMS for Troxyca ER capsules and recommends approval of the proposed REMS.

## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] extended-release (ER) capsules (NDA 207621) and evaluation of Pfizer, Inc. (Pfizer) proposed REMS, received December 19, 2014 and amended on April 1, 2015, July 24, 2015, December 11, 2015, January 8, 2016, May 25, 2016, and June 6, 2016. Pfizer, Inc. (Pfizer) originally submitted NDA 207621 on December 19, 2014 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the reference listed drugs (RLD). The amended NDA submission for Troxyca ER included a proposed REMS document, including appended materials, and REMS supporting document based on the the Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA Opioid Analgesic REMS) (approved on October 23, 2015).

### 1.1 PRODUCT BACKGROUND

Troxyca ER is an opioid agonist/opioid antagonist combination product composed of oxycodone hydrochloride (HCl) and naltrexone HCl. Pfizer's proposed indication for Troxyca ER is, 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 rationale for the development of Troxyca ER is to provide an abuse deterrent formulation of oxycodone which maintains the benefits of an opioid agonist analagesic. Troxyca ER capsules are pellet-filled capsules. The pellets consist of inert seed cores coated with a multiple drug (oxycodone and naltrexone) and polymer layer

[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.

(b) (4) and have a 12% naltrexone HCl to oxycodone HCl ratio by weight. Troxyca ER was shown to have some abuse deterrent properties, due to the combination with naltrexone, when manipulated and administered by the oral, nasal and intravenous (IV) route. It also resists extraction by certain solvents (b) (4)

Oxycodone HCl is an opioid agonist and when formulated as a extended-release product is a part of the ER/LA opioid analgesic drug class. Oxycodone HCl 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 semi-synthetic, 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.

Naltrexone is a centrally acting mu-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors. Naltrexone has few, if any intrinsic actions besides its opioid blocking properties. Naltrexone, administered alone, is not associated with the development of tolerance or dependence, but it will precipitate withdrawal symptoms in subjects physically dependent on opioids. Naltrexone is sequestered within the Troxyca ER capsules and the patient will only be exposed to naltrexone if Troxyca ER is manipulated (crushing, dissolving, etc.).

Pfizer is seeking approval for the following dosage strengths of oxycodone HCl and naltrexone HCl: 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/ 7.2 mg, and 80 mg/9.6 mg. The Troxyca ER capsules are formulated to deliver oxycodone HCl over 12 hours. Pfizer submitted NDA 207621 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLD. The proposed indication for Troxyca ER is consistent with the approved indication for other extended-release formulations of oxycodone (i.e. OxyContin, Targiniq ER), which were all approved under the single, shared system (SSS) REMS for ER/LA opioid analgesic drug products.[2]

Thus, like other ER opioid analgesic products, Troxyca ER poses a risk of abuse/misuse, addiction, overdose and death due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics. ER/LA opioid analgesics are approved under a SSS REMS program. The proposed indication for Troxyca ER is consistent with the products in the SSS REMS for ER/LA opioid analgesic

[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.

drug products. If approved, Troxyca ER will become a part of the SSS ER/LA Opioid Analgesic REMS.

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 Analgesic REMS was approved with the following elements:

- Medication Guide (MG)
- Elements to Assure Safe Use
    - Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics. The following materials are part of the ER/LA Opioid Analgesic REMS and include:
        - 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 19, 2014:** The Sponsor submitted an NDA 207621 for Troxyca ER as a 505(b)(2) application using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLDs. The NDA submission for Troxyca ER included a proposed REMS document, including appended materials, and REMS supporting document based on the ER/LA Opioid Analgesic REMS (approved on August 19, 2014).

**December 29, 2014:** The Agency approved intermediate strengths of fentanyl transdermal systems ANDA 76258, as part of the ER/LA Opioid Analgesic REMS which impacted the FDA Blueprint of the ER/LA Opioid Analgesic REMS.

**March 19, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that includes Troxyca ER product specific information using the currently approved (December 2014) version of the ER/LA Opioid Analgesic REMS.

**April 1, 2015:** The Sponsor submitted a revised version of the December 2014 version of the ER/LA Opioid Analgesic REMS including the REMS document and appended materials and the REMS supporting document. This submission included product-specific information for Troxyca ER.

**April 2, 2015:** The Agency approved revised prescribing information for Dolophine NDA 06134, which impacted the FDA Blueprint of the ER/LA Opioid Analgesic REMS.

**April 29, 2015:** The Division of Medication Error Prevention and Analysis reviewed the Troxyca ER labeling and PI and found them to be acceptable.[3]

**June 26, 2015:** The Agency approved a class wide modification of the ER/LA Opioid Analgesic REMS which included product specific information for Hysingla ER, titration information for Dolophine, and intermediate strengths of fentanyl transdermal systems.

**July 20, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that incorporates Troxyca ER product specific information into the currently approved (June 26, 2015) version of the ER/LA Opioid Analgesic REMS.

**July 24, 2015:** The Sponsor amended the submission, to incorporate Troxyca ER information into the June 26, 2015 version of the ER/LA Opioid Analgesic REMS.

**August 13, 2015:** The Agency approved a REMS Modification for the ER/LA Opioid REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.[4]

**October 2, 2015:** The Agency approved Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA Opioid Analgesic REMS.[5]

**October 23, 2015:** The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA Opioid Analgesic REMS**.**[6]

**December 4, 2015:** The Agency provided comments to the Sponsor on the proposed ER/LA Opioid Analgesic REMS for Troxyca ER.[7]

**December 11, 2015:** The Sponsor amended the submission to include a revised ER/LA Opioid REMS document, REMS appended materials, and the REMS supporting Document , which was based on the ER/LA Opioid Analgesic REMS approved on October 23, 2015, that addressed the Agency's comments from December 4, 2015. This submission is the focus of this review.

**January 8, 2016**: The Sponsor amended the submission to include a revised ER/LA REMS Supporting document.

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

**April 26, 2016:** The Agency approved Xtampza ER (oxycodone extended-release capsule) NDA 208090, as part of the ER/LA Opioid Analgesic REMS.[8]

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[3] Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.

[4] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

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

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

[7] Gonzalez D. DRISK REMS Review for Troxyca ER, dated December 4, 2015.

**May 25, 2016**: The Sponsor amended the submission to include a revised ER/LA Opioid Analgesic REMS for Troxyca ER. However, this submission did not include the recently approved ER/LA Analgesic, Xtampza ER, in the Blueprint. Therefore, the Sponsor was advised, via email, to amend the submission with the correct version of the ER/LA Opioid Analgesic REMS.

**June 6, 2016:** The Sponsor amended their submission to include a revised ER/LA Opioid Analgesic REMS. This submission is the subject of this review.

**June 8, 2016:** Joint meeting of the Anestetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee was held. The Advisory committee voted 9 to approve and 6 to not approve Troxyca ER. The majority of committee members also recommended Troxyca ER should be labeled as an abuse-deterrent product by the nasal(11-yes, 4-No) and intravenous (9-yes, 6-No) route of abuse. The majority of committee members recommended against labeling Troxyca ER as an abuse-deterrent product by the oral (6-yes, 9-No) route of abuse.

# 2 MATERIALS REVIEWED

## 2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 207621 for the proposed ER/LA Opioid Analgesic REMS:

- Pfizer, Inc. Proposed REMS for Troxyca ER, NDA 207621, received December 19, 2014 (ORIG-1; eCTD Sequence No. 0000)
    - Amendment received April 1, 2015 (eCTD Sequence No. 0006)
    - Amendment received July 24, 2015 (eCTD Sequence No. 0017)
    - Amendment received December 11, 2015 (eCTD Sequence No. 0042)
    - Amendment received January 8, 2016 (eCTD Seq. No. 0046)
    - Amendment received May 25, 2016 (eCTD Seq. No. 0048)
    - Amendment received June 6, 2016 (eCTD Seq. No. 0049)

## 2.2 MATERIALS INFORMING OUR REVIEW

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

- Pfizer, Inc. Draft Prescribing Information for Troxyca ER. received September 18, 2015 (ORIG-1; eCTD Sequence No. 0037)
- Extended-Release and Long-Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Kilgore E, Clinical Review for Troxyca ER, dated September 14, 2015.

[8] Approval letter for Xtampza ER (oxycodone extended-release capsule) NDA 208090, dated April 26, 2016.

- Tolliver J. Controlled Substance Staff (CSS) Review for Troxyca ER, dated September 16, 2015.
- Walker M. Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) Review for Troxyca ER, dated September 14, 2015.
- Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.
- Lee K. OPDP. Internal Consult for Troxyca ER, dated December 15, 2015.
- Gonzalez, D. Division of Risk Management (DRISK) Review of the ER/LA Opioid Analgesic REMS for Troxyca ER, dated December 4, 2015.
- Gonzalez, D. Division of Risk Management (DRISK) Review of the ER/LA Opioid Analgesic REMS for Troxyca ER, dated December 18, 2015.
- Gonzalez, D. Division of Risk Management (DRISK) Addendum Review of the ER/LA Opioid Analgesic REMS for Troxyca ER, dated January 15, 2016.

# 3 RESULTS OF REVIEW OF THE PROPOSED REMS FOR TROXCYA ER

The Sponsor proposed to incorporate Troxyca ER into the approved ER/LA Opioid Analgesic REMS. The FDA Blueprint in the ER/LA Opioid Analgesic REMS was impacted. DRISK reviewed Pfizer's proposed REMS, received on June 6, 2016.

## 3.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received June 6, 2016, has no additional changes; 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 Troxyca ER Medication Guide (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]

## 3.3 REMS APPENDED MATERIALS

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

The Sponsor's proposed Patient Counseling Document, received June 6, 2016, has no additional changes; therefore, DRISK finds it acceptable.

[9] Walker M, Patient Labeling Review for Troxyca ER, dated September 14, 2015.

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

The Sponsor's proposed *FDA Blueprint*, received June 6, 2016, includes the previously agreed upon Troxyca ER product specific language.[10] This is the only change to the *FDA Blueprint* beyond what has been approved by the Agency on April 26, 2016; therefore, DRISK finds it acceptable.

### 3.3.3 Prescriber Letters

The Sponsor's proposal, received June 6, 2016, has no additional changes; therefore, DRISK finds them acceptable.

### 3.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, received June 6, 2016, has no additional changes; therefore, DRISK finds them acceptable.

### 3.3.5 ER/LA Opioid Analgesic REMS Website

The Sponsor's proposal, received June 6, 2016, has no additional changes; therefore, DRISK finds them acceptable.

## 3.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The Sponsor's proposal, received June 6, 2016, has no additional changes; therefore, DRISK finds it acceptable.

## 3.5 REMS SUPPORTING DOCUMENT

The Sponsor's proposed REMS Supporting document, received June 6, 2016, has no additional changes; therefore, DRISK finds it acceptable.

# 4 DISCUSSION AND CONCLUSION

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

The Sponsor submitted a proposed REMS for Troxyca ER on June 6, 2016. DRISK finds the proposed ER/LA Opioid REMS (attached) acceptable; therefore, DRISK recommends a approval of the ER/LA Opioid Analgesic REMS as appended to this review.

# 5 RECOMMENDATION

DRISK recommends approval of the ER/LA Opioid Analgesic REMS for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] (NDA 207621), received June 6, 2016 and as appended to this review.

[10] Gonzalaz D. DRISK REMS Review for Troxyca ER, dated December 18, 2015.

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

## 6 ATTACHMENTS

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

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

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/s/

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KIMBERLY LEHRFELD
07/08/2016

CYNTHIA L LACIVITA
07/08/2016
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**

# ADDENDUM TO FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

| | |
|---|---|
| Date: | January 15, 2015 |
| Reviewer(s): | Danny S. Gonzalez, Pharm. D., M.S.,<br>Risk Management Analyst<br>Division of Risk Management (DRISK) |
| Team Leader: | Kim Lehrfeld, Pharm. D.<br>DRISK |
| Director: | Cynthia LaCivita, Pharm. D.<br>DRISK |
| Drug Name(s): | Troxyca ER (oxycodone hydrochloride /naltrexone hydrochloride) |
| Therapeutic Class: | Opioid agonist/opioid antagonist |
| Dosage and Route: | 10 mg/1.2 mg , 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8mg, 60 mg/7.2 mg, and 80 mg/9.6 (oxycodone/naltrexone) abuse-deterrent, extended-release oral capsule |
| Application Type/Number: | NDA 207621 |
| Submission Number: | ORIG-1 |
| Applicant/sponsor: | Pfizer, Inc. |
| OSE RCM #: | 2014-2592; 2014-2593 |

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

This addendum serves to update the previous Final Risk Evaluation and Mitigation Strategy (REMS) Review for Troxyca ER, RCM # 2014-2592 and 2014-2593 dated December 18, 2015.

The REMS supporting document (SD) submitted on December 11, 2015 (Seq. No. 0042), was reviewed by DRISK and documented as correct in DRISK's review on December 19, 2015. However, the Sponsor, Pfizer, Inc., did not provide the most current version of the Extended-Release and Long-Acting Opioid Analgesic (ER/LA) REMS SD and the submission reviewed was inadvertently found to be the correct version of the SD. On December 21, 2015, the Agency requested, via email, that the Sponsor submit the correct version of the ER/LA REMS SD. The Sponsor submitted the correct ER/LA REMS SD on January 8, 2016 (Seq. No. 0046).

Therefore, the Troxyca ER REMS is now considered acceptable to the Office of Surveillance and Epidemiology (OSE), DRISK and DRISK recommends approval of the REMS.

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/s/

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DANNY S GONZALEZ
01/15/2016

CYNTHIA L LACIVITA
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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**

# FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

| | |
|---|---|
| Date: | December 18, 2015 |
| Reviewer(s): | Danny S. Gonzalez, Pharm. D., M.S.,<br>Risk Management Analyst<br>Division of Risk Management (DRISK)<br><br>Donella Fitzgerald, Pharm. D.<br>Risk Management Analyst<br>DRISK |
| Team Leader: | Kim Lehrfeld, Pharm. D.<br>DRISK |
| Director: | Cynthia LaCivita, Pharm. D.<br>DRISK |
| Drug Name(s): | Troxyca ER (oxycodone hydrochloride /naltrexone hydrochloride) |
| Therapeutic Class: | Opioid agonist/opioid antagonist |
| Dosage and Route: | 10 mg/1.2 mg , 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8mg, 60 mg/7.2 mg, and 80 mg/9.6 (oxycodone/naltrexone) abuse-deterrent, extended-release oral capsule |
| Application Type/Number: | NDA 207621 |
| Submission Number: | ORIG-1 |
| Applicant/sponsor: | Pfizer, Inc. |
| OSE RCM #: | 2014-2592; 2014-2593 |

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

# CONTENTS

## EXECUTIVE SUMMARY

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] extended-release (ER) capsules (NDA 207621) and evaluation of Pfizer, Inc. (Pfizer) proposed REMS, received December 19, 2014 and amended on April 1, 2015, July 24, 2015, December 11, 2015. Pfizer submitted NDA 207621 on December 19, 2014 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the reference listed drugs.

If approved, Troxyca ER's risks of abuse/misuse, addiction, overdose and death will be mitigated with labeling and a REMS. Pfizer is currently a member of the the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS for Troxyca ER.[1] DRISK agrees with the Sponsor's proposed REMS for Troxyca ER capsules and recommends approval of the proposed REMS.

## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] extended-release (ER) capsules (NDA 207621) and evaluation of Pfizer, Inc. (Pfizer) proposed REMS, received December 19, 2014 and amended on April 1, 2015, July 24, 2015, and December 11, 2015. Pfizer, Inc. (Pfizer) originally submitted NDA 207621 on December 19, 2014 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the reference listed drugs (RLD). The amended NDA submission for Troxyca ER included a proposed REMS document, including appended materials, and REMS supporting document based on the the Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA Opioid Analgesic REMS) (approved on October 23, 2015).

### 1.1 PRODUCT BACKGROUND

Troxyca ER is an opioid agonist/opioid antagonist combination product composed of oxycodone hydrochloride (HCl) and naltrexone HCl. Pfizer's proposed indication for Troxyca ER is, 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 rationale for the development of Troxyca ER is to provide an abuse deterrent formulation of oxycodone which maintains the benefits of an opioid agonist analagesic. Troxyca ER capsules are pellet-filled capsules. The pellets consist of inert seed cores coated with a multiple drug (oxycodone and naltrexone) and polymer layer (b) (4) and have a 12% naltrexone HCl to oxycodone HCl ratio by weight. Troxyca ER was shown to have some abuse deterrent properties, due to the combination with naltrexone, when manipulated and administered

[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.

by the oral, nasal and intravenous (IV) route. It also resists extraction by certain solvents [redacted] (b) (4) See sections 3.1.2 Efficacy of the abuse deterrent properties of Troxyca ER.

Oxycodone HCl is an opioid agonist and when formulated as a extended-release product is a part of the ER/LA opioid analgesic drug class. Oxycodone HCl 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 semi-synthetic, 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.

Naltrexone is a centrally acting mu-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors. Naltrexone has few, if any intrinsic actions besides its opioid blocking properties. Naltrexone, administered alone, is not associated with the development of tolerance or dependence, but it will precipitate withdrawal symptoms in subjects physically dependent on opioids. Naltrexone is sequestered within the Troxyca ER capsules and the patient will only be exposed to naltrexone if Troxyca ER is manipulated (crushing, dissolving, etc.).

Pfizer is seeking approval for the following dosage strengths of oxycodone HCl and naltrexone HCl: 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/ 7.2 mg, and 80 mg/9.6 mg. The Troxyca ER capsules are formulated to deliver oxycodone HCl over 12 hours. Pfizer submitted NDA 207621 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLD. The proposed indication for Troxyca ER is consistent with the approved indication for other extended release formulations of oxycodone (i.e. OxyContin, Targiniq ER), which were all approved under the single, shared system (SSS) REMS for ER/LA opioid analgesic drug products.[2]

Thus, like other ER opioid analgesic products, Troxyca ER poses a risk of abuse/misuse, addiction, overdose and death due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics. ER/LA opioid analgesics are approved under a SSS REMS program. The proposed indication for Troxyca ER is consistent with the products in the SSS REMS for ER/LA opioid analgesic drug products. If approved, Troxyca ER will become a part of the SSS ER/LA Opioid Analgesic REMS.

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[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.

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 Analgesic REMS was approved with the following elements:

- Medication Guide (MG)
- Elements to Assure Safe Use
    - Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics. The following materials are part of the ER/LA Opioid Analgesic REMS and include:
        - 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 19, 2014:** The Sponsor submitted an NDA 207621 for Troxyca ER as a 505(b)(2) application using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLDs. The NDA submission for Troxyca ER included a proposed REMS document, including appended materials, and REMS supporting document based on the ER/LA Opioid Analgesic REMS (approved on August 19, 2014).

**December 29, 2014:** The Agency approved intermediate strengths of fentanyl transdermal systems ANDA 76258, as part of the ER/LA Opioid Analgesic REMS which impacted the FDA Blueprint of the ER/LA Opioid Analgesic REMS.

**March 19, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that includes Troxyca ER product specific information using the currently approved (December 2014) version of the ER/LA Opioid Analgesic REMS.

**April 1, 2015:** The Sponsor submitted a revised version of the December 2014 version of the ER/LA Opioid Analgesic REMS including the REMS document and appended materials and the REMS supporting document. This submission included product-specific information for Troxyca ER.

**April 2, 2015:** The Agency approved revised prescribing information for Dolophine NDA 06134, which impacted the FDA Blueprint of the ER/LA Opioid Analgesic REMS.

**April 29, 2015:** The Division of Medication Error Prevention and Analysis reviewed the Troxyca ER labeling and PI and found them to be acceptable.[3]

**June 26, 2015:** The Agency approved a class wide modification of the ER/LA Opioid Analgesic REMS which included product specific information for Hysingla ER, titration information for Dolophine, and intermediate strengths of fentanyl transdermal systems.

**July 20, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that incorporates Troxyca ER product specific information into the currently approved (June 26, 2015) version of the ER/LA Opioid Analgesic REMS.

**July 24, 2015:** The Sponsor amended the submission, to incorporate Troxyca ER information into the June 26, 2015 version of the ER/LA Opioid Analgesic REMS.

**August 13, 2015:** The Agency approved a REMS Modification for the ER/LA Opioid REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.[4]

**October 2, 2015:** The Agency approved Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA Opioid Analgesic REMS.[5]

**October 23, 2015:** The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA Opioid Analgesic REMS**.**[6]

**December 4, 2015:** The Agency provided comments to the Sponsor on the proposed ER/LA Opioid Analgesic REMS for Troxyca ER.[7]

**December 11, 2015:** The Sponsor amended the submission to include a revised ER/LA Opioid REMS document, REMS appended materials, and the REMS supporting document , which was based on the ER/LA Opioid Analgesic REMS approved on October 23, 2015, that addressed the Agency's comments from December 4, 2015. 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 207621 for the proposed ER/LA Opioid Analgesic REMS:

- Pfizer, Inc. Proposed REMS for Troxyca ER, NDA 207621, received December 19, 2014 (ORIG-1; eCTD Sequence No. 0000)
    - Amendment received April 1, 2015 (eCTD Sequence No. 0006)

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[3] Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.

[4] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

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

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

[7] Gonzalez D. DRISK REMS Review for Troxyca ER, dated December 4, 2015.

- Amendment received July 24, 2015 (eCTD Sequence No. 0017)
- Amendment received December 11, 2015 (eCTD Sequence No. 0042)

### 2.2 MATERIALS INFORMING OUR REVIEW

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

- Pfizer, Inc. Draft Prescribing Information for Troxyca ER. received September 18, 2015 (ORIG-1; eCTD Sequence No. 0037)
- Extended-Release and Long-Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Kilgore E, Clinical Review for Troxyca ER, dated September 14, 2015.
- Tolliver J. Controlled Substance Staff (CSS) Review for Troxyca ER, dated September 16, 2015.
- Walker M. Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) Review for Troxyca ER, dated September 14, 2015.
- Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.
- Lee K. OPDP. Internal Consult for Troxyca ER, dated December 15, 2015.

## 3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The Sponsor conducted a clinical development program for Troxyca ER, consisting of 14 clinical studies including two Phase 3 efficacy and safety studies in patients with moderate-to-severe chronic pain, 5 pharmacodynamic (PD) studies conducted in non-dependent recreational opioid users (2 studies determined the naltrexone to oxycodone dose ratio and 3 studies evaluated abuse potential of the Troxyca ER formulation), and 7 clinical pharmacology and pharmacokinetic (PK) studies in healthy volunteers to support the safety and efficacy of Troxyca ER.

### 3.1 SUMMARY OF EFFICACY

#### 3.1.1 Efficacy of Troxyca ER for the management of pain

The sponsor sought to establish analgesic efficacy results with two phase 3 clinical studies (B4531002, B4531001).

The first study, B4531002, was a multicenter, 12 week, double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of Troxyca ER compared to placebo in opioid-naïve and opioid-experienced subjects with moderate-to-severe chronic lower back pain (CLBP). Study B4531002 included an open-label conversion and titration period enrichment phase and a double-blind randomized withdrawal phase. The enrichment phase participants began with open-label Troxyca ER, which was titrated to effectiveness. Subjects who tolerated treatment and achieved satisfactory efficacy with Troxyca ER were randomized to continue Troxyca ER or be

switched to placebo for a comparison of efficacy and adverse effects during the double-blind randomized withdrawal phase.

A total of 410 people entered the titration phase and received at least one dose of Troxyca ER, however, 280 (134 placebo, 146 Troxyca ER) were randomized and treated in the double-blind period. The remaining 129 subjects discontinued the study, with the most common reasons reported to be adverse effects (AE, 13.9%) and inability to meet entrance criteria for the treatment period (10.0%). For those that did continue through the treatment phase, the dosages supplied for Troxyca ER included: 10mg/1.2mg, 20mg/2.4mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60 mg/7.2mg and 80mg/9.6mg. The capsules were taken in the morning and evening, approximately 12 hours apart.

The primary efficacy endpoint in the study was the difference between the mean changes in the daily average Numerical Rating Scale pain scores for lower back pain from randomization baseline, to the average of the scores from the final two weeks of the double-blind treatment period when comparing Troxyca ER versus placebo. Upon completion of the study, researchers saw a least square (LS) mean treatment difference of -0.62, with a p value of 0.0114. This demonstrated that Troxyca ER provided a statistically significant improvement in lower back pain compared to placebo from baseline to the average score of the final two weeks of treatment.

The second study, B4531001, was a multicenter, 12 month, open-label, single-arm safety study of Troxyca ER used in subjects with moderate-to-severe chronic non-cancer pain (CNCP). Even though this was a safety study, assessments of analgesic efficacy were secondary endpoints. Over the course of 12 months, 158 subjects with moderate-to-severe CNCP were repeatedly dosed with Troxyca ER. The total daily dose of the oxycodone component ranged from 20 to 160 mg, given at 12 or 24 hour intervals. The subject's pain intensity was evaluated using the Brief Pain-Inventory-short form (BPI-sf) questionnaire. At the end of the study, it was observed that the mean percent decrease from baseline for BPI-sf average pain was statistically different ($p \leq 0.0003$) from zero at all visits, although conclusions are limited due to the open-label design and lack of a comparator group. The clinical reviewer stated that these studies were adequate to establish efficacy.[8]

### 3.1.2 Efficacy of the abuse deterrent properties of Troxyca ER[9]

The efficacy of the abuse-deterrent properties of Troxyca ER were evaluated in five clinical trials conducted in 167 subjects. Two dose ratio trials (07-201, 09-2001) were conducted to determine the best ratio of oxycodone to naltrexone to mitigate abuse. Category 1 in-vitro extraction trials were conducted on intact and crushed Troxyca ER pellets of the proposed commercial formulation to determine conditions under which oxycodone can be rapidly extracted separately from naltrexone for abuse purposes. Additionally, three Category 2 (PK)/Category 3 (pharmacodynamic-human abuse potential) trials were conducted to examine the abuse potential of manipulated Troxyca ER by oral (B4531008), intranasal (B4531009), and simulated IV (B4981002) routes.



[8] Kilgore E, Clinical Review for Troxyca. September 14, 2015.

[9] Tolliver J. Controlled Substance Staff Review for Troxyca, September 16, 2015.

**Dose Ratio Trials:**

Studies Troxyca ER-07-201 and Troxyca ER-09-2001 were conducted to evaluate the pharmacodynamic (PD) effects of different percentages of commercially available naltrexone HCl to oxycodone HCl in non-dependent subjects with a history of recreational opioid use. There were a total of 61 subjects who participated in the two studies. The investigators found that the optimal combination for reduction in abuse potential was a 12% naltrexone/oxycodone ratio.

**Category 1 – Laboratory Manipulation and Extraction Studies**

Comprehensive in-vitro extraction studies were performed on intact and crushed Troxyca ER pellets to determine conditions under which oxycodone can be rapidly extracted for abuse.


**Category 3 - Clinical Abuse Potential Trials of Manipulated Troxyca ER**

Three trials (B4531008, B4531009, and B4981002) were conducted to examine the clinical abuse-potential of manipulated Troxyca ER . All of these studies were randomized, single-dose, double-blind, cross-over, placebo and active-controlled studies in a total of 106 healthy subjects who were non-dependent, recreational opioid users.

B4531008-Oral Abuse Potential: Thirty-two subjects underwent six 3-day inpatient treatment sessions where they received 40 and 60 mg of immediate-release (IR) oxycodone, 40 mg/4.8 and 60 mg/7.2 mg of crushed Troxyca ER pellets, 60 mg/7.2 mg intact Troxyca ER and placebo. Primary endpoints were $E_{max}$ and $AUE_{0-2h}$ on the 100 point bipolar VAS for Drug Liking and the 100 point unipolar VAS for High. The results of this study indicated that crushed and intact Troxyca ER demonstrated significantly lower values than crushed IR oxycodone and significantly higher values than placebo, with the exception of intact Troxyca ER 60 mg/7.2 mg compared to placebo for $AUE_{0-2h}$ for both Drug Liking and High.

B4531009-Crushed Intranasal Abuse Potential: Twenty-eight subjects underwent four 3-day inpatient treatment sessions where they received crushed IR oxycodone 30 mg, crushed Troxyca ER 30mg/3.6 mg pellets and crushed weight matched placebos. Primary endpoints were the same as study B45310008: VAS for Drug-Liking and High, summarized by $E_{max}$ and $AUE_{0-2h}$. The study results indicated that crushed Troxyca ER (30 mg/3.6 mg) showed significantly lower responses for both Drug-Liking and High for the $E_{max}$ and $AUE_{0-2h}$ compared to crushed IR oxycodone when taken intranasally.

B4981002 -Crushed [Simulated IV] Abuse Potential: Twenty-nine subjects underwent three 3-day inpatient treatment sessions where they received IV administration of 20 mg oxycodone, 20 mg oxycodone concomitantly with 2.4 mg of naltrexone and placebo. Primary endpoints once again, were VAS for Drug-Liking and High, summarized by $E_{max}$ and $AUE_{0-2h}$. The results of this study indicated that IV administration of simulated crushed Troxyca ER demonstrated significantly lower values than IV oxycodone and significantly higher values than placebo, with the exception of simulated crushed Troxyca ER compared to placebo for $AUE_{0-2h}$ for Drug-Liking.

For all three of the above clinical abuse trials (B4531008, B4531009, B4981002) the mean and median peak Drug-Liking and High scores were significantly lower ($p \leq 0.0002$) for Troxyca ER compared to oxycodone.

### 3.2 SUMMARY OF SAFETY

Safety of Troxyca ER was evaluated primarily through examination of the two Phase 3 studies (B4531001, B4531002). Information on safety and tolerability was also contributed from the 5 dose ratio/abuse potential and 7 PK studies (section 3.1.2). During the course of the clinical development program, Troxyca ER was administered in doses ranging from 10mg/1.2 mg up to 80 mg/9.6 mg twice daily for up to 12 months. The total safety population (n = 1085) consisted of individuals who were exposed to at least one dose of Troxyca ER during the clinical development program.

There was one death observed while taking Troxyca ER during the clinical program, and one death reported a year after completion of a subject's last dose. In Study B4531001, the subject died from an acute myocardial infarction, two months after starting the trial. The second death, caused by squamous cell cancer, was reported approximately one year after subject's last dose of Troxyca ER. As noted by the clinical investigators, neither death was considered to be related to the study medication.

In the Phase 3 studies (B4531001, B4531002), for which there were 805 participants, the adverse reaction data was divided into titration, maintenance and long-term maintenance phase pools. All SAE reported during the titration phase were considered unrelated to the study medication, with the exception of a cerebrovascular accident for which there was no data. During the maintenance phase there were two SAE that were attributed to Troxyca ER use, cholelithiasis and abdominal pain. Though the abdominal pain resolved, the cholelithiasis did not. The development of cholelithiasis is likely due to the naltrexone in the formulation, as it has previously been associated with gall bladder adverse effects.[10] Abdominal pain was also reported in the long term maintenance phase as a medication related SAE. The subject did recover and the pain resolved. No other SAE was attributable to the study drug for this safety pool.

The most frequently reported treatment emergent adverse effects (TEAEs) in general, were nausea, constipation, vomiting, somnolence, headache and dizziness. They were all reported in $\geq$ 5% of the combined phase 3 study population and are commonly associated with opioid use.

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[10] Kjome K, Moeller F. Long-Acting Injectable Naltrexone for the Management of Patients with Opioid Dependence. Subst Abuse. 2011; 5: 1–9.

Nausea was the number one reason cited for study discontinuation during the titration (4.2%) and maintenance phases (1.4%) of the clinical trials, but was not reported as a cause of study drop-out during the long term maintenance phases. Constipation was the second most reported cause of study discontinuation, with 2.0% during titration and zero during maintenance. The third leading cause was vomiting with 1.9% during titration and zero during maintenance. These AEs are consistent with the findings of the opioid class.

The clinical reviewer concluded that there were no deaths definitely or probably attributable to Troxyca ER and no unexpected or unusual adverse events of special interest were identified to suggest a safety signal or trend. It is not definitive, however, whether the increased incidence of withdrawal in Troxyca ER-treated subjects compared to placebo is due to the inclusion of naltrexone. Most cases identified as drug withdrawal syndrome were mild to moderate in severity, resolved spontaneously, and did not require intervention. Most of the subjects experiencing withdrawal also had other reasons to have experienced opioid withdrawal, such as dose adjustment due to tapering, conversion, or noncompliance. The exact relationship of systemic naltrexone or naltrexol in precipitating opioid withdrawal is unclear. The profile of adverse events was, otherwise, generally consistent with a mu-opioid agonist. The dosing recommendations are acceptable based on the data from the clinical development program.[2]

## 4 RATIONALE FOR A REMS FOR TROXYCA ER

DRISK agrees with the Sponsor and the Division of Anesthesia, Analgesia, and Addiction Products (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 Troxyca ER. While all opioid formulations have the potential for these risks, based on currently available data, the Agency believes that ER/LA opioid analgesics 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.

Troxyca ER includes an abuse deterrent formulation that may mitigate the risk of adverse events if manipulated and administered by the oral, nasal and IV route. It also resists extraction by certain mechanisms. Also, the combination with naltrexone mitigates the risk of intervenous abuse. However, Troxyca ER contains oxycodone HCl in doses which could potentially result in overdose or death due to the high amounts of oxycodone HCl. 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, Troxyca 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 Troxyca ER to join the single, shared system ER/LA Opioid REMS.

# 5 RESULTS OF REVIEW OF THE PROPOSED REMS FOR TROXCYA ER

The Sponsor proposed to incorporate Troxyca ER into the approved ER/LA Opioid Analgesic REMS. This modification impacted the ER/LA Opioid Analgesic REMS appended materials including the FDA Blueprint. DRISK and OPDP[11] reviewed Pfizer's proposed REMS, received on December 11, 2015, in response to comments from the Agency provided on December 4, 2015.[12]

OPDP was consulted to review the ER/LA REMS materials related to Troxyca on July 28, 2015.[11] DRISK notes that OPDP provided the following comments in their December 15, 2015 review of Troxyca, with which DRISK agrees:

> *OPDP does not object to the modifications made to the following materials:*
>
> *• Patient Counseling Document (PCD) on Extended Release/Long Acting Opioid Analgesics*
>
> *• FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*
>
> *• Prescriber Letter #3*
>
> *• ER/LA Opioid Analgesic REMS SSS website (screen shots for www.ERLA-opioidREMS.com )*
>
> *OPDP notes that no changes were proposed for the Prescriber Letters #1 and #2 and the Professional Organization/Licensing Board Letters. We have no additional comments on these proposed REMS materials at this time.*

## 5.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received December 11, 2015 has no additional changes; therefore, DRISK finds it acceptable.

## 5.2 MEDICATION GUIDE

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Troxyca ER Medication Guide (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.[13]

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[11] Lee K. OPDP. Internal Consult for Troxyca ER, dated December 15, 2015.

[12] Gonzalez D. DRISK REMS Review for Troxyca ER, dated December 4, 2015

[13] Walker M, Patient Labeling Review for Troxyca ER, dated September 14, 2015.

### 5.3 REMS Appended Materials

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

The Sponsor included the Agency's feedback in the Patient Counseling Document and proposed no additional changes. DRISK and DAAAP find the proposed changes, received December 11, 2015, that incorporate the Agency's feedback acceptable.

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

The Sponsor proposed to include Troxyca ER product-specific language in the FDA Blueprint. DRISK and DAAAP find the proposed changes, received December 11, 2015, that incorporate the Agency's feedback acceptable.

#### 5.3.3 Prescriber Letters

The Sponsor included the Agency's feedback in the Prescriber Letters and proposed no additional changes. DRISK and DAAAP find the proposed changes, received December 11, 2015, that incorporate the Agency's feedback acceptable.

#### 5.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, received December 11, 2015 has no additional changes; therefore, DRISK finds them acceptable.

#### 5.3.5 ER/LA Opioid Analgesic REMS Website

The Sponsor included the Agency's feedback in the REMS website and proposed no additional changes. DRISK and DAAAP find the proposed changes, received December 11, 2015, that incorporate the Agency's feedback acceptable.

### 5.4 Timetable for Submission of Assessments

The Sponsor's proposal, received December 11, 2015, has no additional changes; therefore, DRISK finds it acceptable.

### 5.5 REMS SUPPORTING DOCUMENT

The Sponsor's proposed REMS supporting document, received December 11, 2015 has no additional changes; therefore, DRISK finds it acceptable.

## 6 DISCUSSION AND CONCLUSION

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

The Sponsor submitted a proposed REMS for Troxyca ER on December 11, 2015 based on the Agency's comments.[14] DRISK finds the proposed ER/LA Opioid REMS (attached) acceptable; therefore, DRISK recommends a approval of the ER/LA Opioid Analgesic REMS as appended to this review.

## 7 RECOMMENDATION

DRISK recommends approval of the ER/LA Opioid Analgesic REMS for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] (NDA 207621), received December 11, 2015 and as appended to this review.

A REMS Modification Notification Letter should be sent to the other members of the ER/LA Opioid Analgesic 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

[14] Gonzalez D. DRISK REMS Review for Troxcya ER, dated December 4, 2015

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

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

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/s/

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DANNY S GONZALEZ
12/18/2015

CYNTHIA L LACIVITA
12/18/2015
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**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

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| Date: | December 4, 2015 |
| Reviewer(s): | Danny S. Gonzalez, Pharm. D., M.S.,<br>Risk Management Analyst<br>Division of Risk Management (DRISK)<br><br>Joan Blair, R.N., M.P.H.<br>Health Communication Analyst<br>DRISK |
| Team Leader: | Kim Lehrfeld, Pharm. D.<br>DRISK |
| Director: | Cynthia LaCivita, Pharm. D.<br>DRISK |
| Drug Name(s): | Troxyca ER (oxycodone hydrochloride /naltrexone hydrochloride) |
| Therapeutic Class: | Opioid agonist/ opioid antagonist |
| Dosage and Route: | 10 mg/1.2 mg , 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8mg, 60 mg/7.2 mg, and 80 mg/9.6 (oxycodone/naltrexone)<br>abuse-deterrent, extended-release oral capsule |
| Application Type/Number: | NDA 207621 |
| Submission Number: | ORIG-1 |
| Applicant/sponsor: | Pfizer, Inc. |
| OSE RCM #: | 2014-2592; 2014-2593 |

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

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# 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of Pfizer, Inc.'s (Pfizer) risk evaluation and mitigation strategy (REMS) submission, received December 19, 2014 and amended on April 1, 2015 and July 24, 2015. Pfizer is submitting a NDA under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the reference listed drugs (RLD). The Sponsor is currently a member in the REMS Program Companies (RPC). On July 24, 2015, Pfizer submitted a proposal which included Troxyca ER in the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* of the Extended-Release and Long-Acting Opioid Analgesic REMS (ER/LA Opioid REMS). This submission is the focus of this review.

## 1.1 PRODUCT BACKGROUND

Troxyca ER is an opioid agonist/opioid antagonist combination product composed of oxycodone hydrochloride (HCl) and naltrexone HCl. Troxyca ER has a 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. The rationale for the development of Troxyca ER is to provide an abuse deterrent formulation of oxycodone which maintains the benefits of an opioid agonist. Troxyca ER capsules are pellet-filled capsules (b) (4) The pellets consist of inert seed cores coated with a multiple drug (oxycodone and naltrexone) and polymer layer (b) (4) and have a 12% naltrexone HCl to oxycodone HCl ratio by weight. Troxyca ER was shown to have some abuse deterrent properties, due to the combination with naltrexone, when manipulated and administered by the oral, nasal and intravenous (IV) route. It also resists extraction by certain mechanisms.

Oxycodone HCl is an opioid agonist that is a part of the ER/LA opioid analgesic drug class when formulated as a extended-release product. Oxycodone HCl 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 semi-synthetic, 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. Naltrexone is a centrally acting mu-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors. Naltrexone has few, if any intrinsic actions besides its opioid blocking properties. Naltrexone, administered alone, is not associated with the development of tolerance or dependence, but it will precipitate withdrawal

symptoms in subjects physically dependent on opioids. Naltrexone is sequestered within the Troxyca ER capsules and the patient will only be exposed to naltrexone if Troxyca ER is manipulated (crushing, dissolving, etc.).

Pfizer is seeking approval for the following dosage strengths of oxycodone HCl and naltrexone HCl: 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/ 7.2 mg, and 80 mg/9.6 mg. The Troxyca ER capsules are formulated to deliver oxycodone HCl over 12 hours. Pfizer submitted NDA 207621 under section 505(b)(2) using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLD. The proposed indication for Troxyca ER is consistent with the approved indication for other extended release formulations of oxycodone (i.e. OxyContin, Targiniq ER), which were all approved under the single shared system (SSS) REMS for ER/LA opioid analgesic drug products.[1]

Thus, like other extended-release opioid products, Troxyca ER 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 SSS REMS program. The proposed indication for Troxyca ER is consistent with the products in the SSS REMS for extended-release/long-acting (ER/LA) opioid analgesic drug products. If approved Troxyca ER will become a part of the SSS ER/LA Opioid REMS.

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 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

[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.

**December 19, 2014:** The Sponsor submitted an NDA 207621 for Troxyca ER as a 505(b)(2) application using Teva Womens Health Inc.'s Revia (naltrexone - NDA 018932) and Mallinckrodt Inc.'s Roxicodone (oxycodone HCl - NDA 021011) as the RLDs. The NDA submission for Troxyca ER included a proposed REMS document, including appended materials, and REMS supporting document based on the ER/LA Opioid REMS (approved on August 19, 2014).

**December 29, 2014:** The Agency approved intermediate strengths of fentanyl transdermal systems ANDA 76258, as part of the ER/LA Opioid REMS which impacted the FDA Blueprint of the ER/LA Opioid REMS.

**March 19, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that includes Troxyca ER product specific information using the currently approved (December 2014) version of the ER/LA Opioid REMS.

**April 1, 2015:** The Sponsor submitted a revised version of the December 2014 version of the ER/LA Opioid REMS including the REMS document and appended materials and the REMS supporting document. This submission included product-specific information for Troxyca ER.

**April 2, 2015:** The Agency approved revised prescribing information for Dolophine NDA 06134, which impacted the FDA Blueprint of the ER/LA Opioid REMS.

**April 29, 2015:** The Division of Medication Error Prevention and Analysis reviewed the Troxyca ER labeling and PI and found them to be acceptable.[2]

**June 26, 2015:** The Agency approved a class wide modification of the ER/LA Opioid REMS which included product specific information for Hysingla ER, titration information for Dolophine, and intermediate strengths of fentanyl transdermal systems.

**July 20, 2015:** The Agency issued an Information Request for the submission of an ER/LA Opioid REMS that incorporates Troxyca ER product specific information into the currently approved (June 26, 2015) version of the ER/LA Opioid REMS.

**July 24, 2015:** The Sponsor amended the submission, to incorporate Troxyca ER information into the June 26, 2015 version of the ER/LA Opioid REMS.

**August 13, 2015:** The Agency approved a REMS Modification for the ER/LA Opioid REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.[3]

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

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[2] Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.

[3] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

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

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

# 2 MATERIALS REVIEWED

## 2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 207621 for the proposed ER/LA Opioid REMS:

- Pfizer, Inc. Proposed REMS for Troxyca ER, NDA 207621, received December 19, 2014 (ORIG-1; eCTD Sequence No. 0000)
    - Amendment received April 1, 2015 (eCTD Sequence No. 0006)
    - Amendment received July 24, 2015 (eCTD Sequence No. 0017)

## 2.2 MATERIALS INFORMING OUR REVIEW

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

- Pfizer, Inc. Draft Prescribing Information for Troxyca ER. received September 18, 2015 (ORIG-1; eCTD Sequence No. 0037)
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Kilgore E, Clinical Review for Troxyca ER, dated September 14, 2015.
- Tolliver J. Controlled Substance Staff (CSS) Review for Troxyca ER, dated September 16, 2015.
- Walker M. Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) Review for Troxyca ER, dated September 14, 2015.
- Schlick J. Division of Medication Error Prevention and Analysis Review for Troxyca ER, dated April 29, 2015.

# 3 DRISKS'S EVALUATION OF THE PROPOSED REMS

## 3.1 MEDICATION GUIDE

The OPDP/PLRT reviewed the Sponsor's proposed Troxcya ER MG under separate cover and has communicated their recommendations to DAAAP. OPDP/PLRT has found the MG to be acceptable.[6]

## 3.2 REMS DOCUMENT

The Sponsor's proposed REMS document, originally received December 19, 2014 and re-submitted July 24, 2015, has no additional changes; therefore, DRISK finds them acceptable.

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

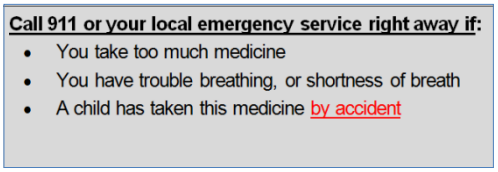
[6] Walker M. Patient Labeling Review for Troxyca ER, dated September 14, 2015.

## 3.3 APPENDED MATERIALS

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

The Sponsor's proposed REMS document, originally received December 19, 2014 and re-submitted July 24, 2015, has no additional changes. DRISK does not find this submission to be acceptable.

*DRISK Comments: DRISK and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) have reviewed the submission and have the following revisions to the Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (see below). This will align this material with changes made in the REMS modification for the OxyContin pediatric indication.*[7]



**Call 911 or your local emergency service right away if:**

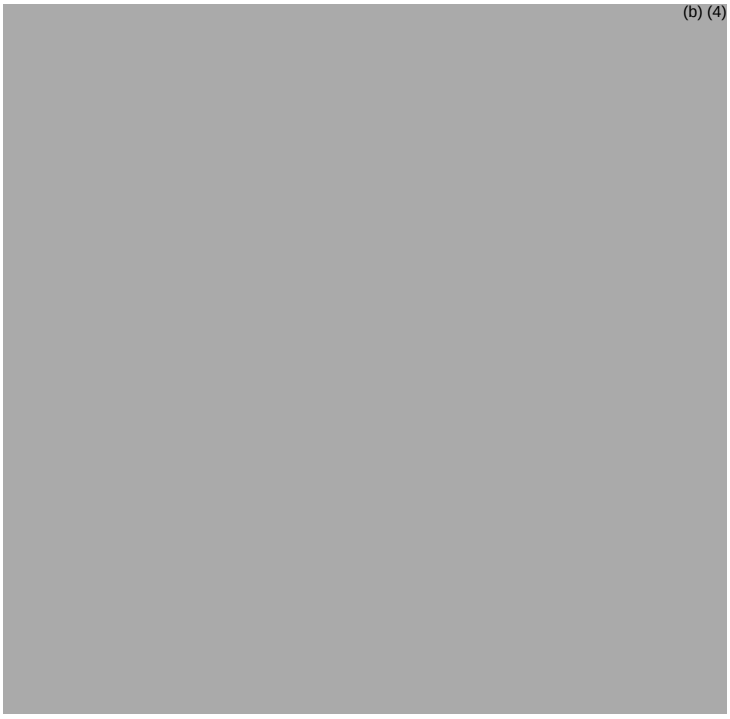
- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine by accident

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

The Sponsor's proposal, originally received December 19, 2014 and re-submitted July 24, 2015, incorporates the Troxyca ER product-specific information in to the ER/LA Blueprint. DRISK does not find this submission to be acceptable.

*DRISK Comments: DRISK and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) have reviewed the submission and have the following revisions to the Troxyca ER product-specific information in the Blueprint(see below).*

[7] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.




*Since the Sponsor's last REMS submission, there have also been several approved modifications to the ER/LA Opioid REMS impacting the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics that need to be included in the Sponsor's re-submission. These revisions are summarized below and are included in the redlined, attached materials:*

- ***August 13, 2015:*** *The Agency approved a REMS Modification for the ER/LA Opioid REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.[8]The FDA Blueprint, the Patient Counseling document and REMS Website were impacted.*
- ***October 2, 2015:*** *The Agency approved a new ER/LA product, Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA Opioid REMS.[9] The FDA Blueprint was impacted.*
- ***October 23, 2015:****The Agency approved a new ER/LA product, Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA Opioid REMS. The FDA Blueprint, Prescriber letters and REMS Website were impacted.[10]*

[8] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

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

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

### 3.3.3 Prescriber Letters

The Sponsor's proposal, originally received December 19, 2014 and re-submitted July 24, 2015, has no additional changes. DRISK does not find this submission to be acceptable.

*Reviewer Comment: The addition of Belbuca to the ER/LA Opioid REMS requires the following revision to these letters.*[11]

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*
- 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 19, 2014 and re-submitted July 24, 2015, has no additional changes; therefore, DRISK finds them acceptable.

### 3.3.5 ER/LA Opioid Analgesic REMS website

The Sponsor's proposal, originally received received December 19, 2014 and re-submitted July 24, 2015 has no additional changes. DRISK does not find this submission to be acceptable.

*Reviewer Comment: The additions of the new indication for OxyContin*[12] *and the approval of Belbuca*[9] *to the ER/LA Opioid REMS required the following revision to the Important Safety Information on the ER/LA Opioid 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.

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

[12] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol 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. Extended-release oxycodone (OxyContin) is also indicated in pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent. **ER/LA opioid analgesics are not indicated for acute pain.**

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve ER/LA opioid analgesics reserved for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise be inadequate to provide sufficient management of pain. (b) (4)

(b) (4)

(b) (4) For some of the ER/LA opioid analgesics, certain (b) (4) strengths (b) (4) certain daily doses, and in specific indicated patient populations (e.g., pediatric patients) are for use in opioid-tolerant patients only. Consult the individual Full Prescribing Information for the definition of opioid tolerance and dosing instructions for patients. (b) (4)

(b) (4) ER/LA opioid analgesics are not intended for acute pain, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.

(b) (4)

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. (b) (4)

(b) (4) **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to this REMS designed to facilitate important discussions with your patients and their caregivers for whom you select an ER/LA opioid analgesic. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely—out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients and their caregivers to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

## 3.4 REMS SUPPORTING DOCUMENT

The Sponsor's proposed REMS supporting document, originally received December 19, 2014 and re-submitted July 24, 2015, has no additional changes. DRISK does not find this submission to be acceptable.

*Reviewer Comment: The approvals of the new indication for OxyContin[13] and Belbuca[14] require revisions to the ER/LA Opioid REMS supporting document.*

[13] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

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

## 4 CONCLUSION AND RECOMMENDATION

DRISK recommends that Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] 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 OxyContin (approved on August 13, 2015), Morphabond (approved on October 2, 2015), and Belbuca (approved on October 23, 2015) as part of the ER/LA Opioid REMS, must also be incorporated into the ERLA REMS materials (Blueprint, Patient Counseling Document, 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 document and appended materials for Troxyca ER [oxycodone hydrochloride (HCl) and naltrexone HCl] capsule (NDA 207621) 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 December 10, 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 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. Please respond to these comments by December 10, 2015 to facilitate further review for this submission.

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: OxyContin (approved on August 13, 2015), Morphabond (approved on October 2, 2015), and Belbuca (approved on October 23, 2015) were approved by the Agency with a revised ER/LA Opioid REMS. The attached ER/LA Opioid REMS materials includes OxyContin, Morphabond, and Belbuca's product-specific information in the Blueprint, Patient Counseling Document, Prescriber Letters and Website where noted. If approved, Troxyca ER's REMS must include OxyContin, Morphabond, and Belbuca's product specific 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. Submit the following materials, and any other materials with additional proposed revisions not listed here, as a redlined, Word document and as a clean, final, formatted PDF document:
    i. Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics
    ii. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
    iii. Prescriber Letters
    iv. ER/LA Opioid Analgesic REMS website
b. Submit the following materials (which were not revised) as clean, final, formatted Word and PDF documents
    i. ER/LA Opioid REMS Document
    ii. Professional Organization/Licensing Board Letters

**APPENDIX**

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

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

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

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/s/

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DANNY S GONZALEZ
12/04/2015

KIMBERLY LEHRFELD
12/04/2015