

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204031Orig1s000

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 28, 2014

Reviewer(s): Jamie Wilkins Parker, Pharm.D.
Division of Risk Management

Team Leader: Reema Mehta, Pharm.D., M.P.H.
Division of Risk Management
Kim Lehrfeld, Pharm.D.
Division of Risk Management

Division Director: Claudia Manzo, Pharm.D.
Division of Risk Management

Drug Name(s): Xartemis XR (oxycodone and acetaminophen)

Therapeutic Class: Opioid Agonist

Dosage and Route: 7.5 mg oxycodone hydrochloride and
325 mg acetaminophen oral tablets

Application Type/Number: NDA 204-031

Applicant/sponsor: Mallinckrodt, Inc.

OSE RCM #: 2013-1253

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

1 INTRODUCTION

The purpose of this document is to provide the Division of Risk Management's (DRISK's) assessment of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Xartemis XR (oxycodone/acetaminophen) oral tablets, NDA 204031. The Sponsor, Mallinckrodt, Inc., submitted a proposed REMS on May 23, 2013, which integrated Xartemis XR into the approved Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS. The NDA is currently under review in the Division of Anesthesia, Analgesia and Addiction Products (DAAAP).

1.1 BACKGROUND

Xartemis XR (oxycodone HCl and acetaminophen), a combination product, is proposed by the Sponsor for the management of (b) (4) acute pain where use of an opioid analgesic is appropriate. Oxycodone is an opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. Acetaminophen is a non-opiate, non-salicylate analgesic, and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined.

Xartemis XR is a Schedule II, extended-release tablet containing 7.5mg oxycodone HCL and 325mg acetaminophen for twice daily oral administration composed of both immediate- and extended-release components. The product utilizes Depomed's AcuForm™ gastroretentive (GR) drug delivery technology. The AcuForm GR technology targets the release of active pharmaceutical ingredient (API) in the upper gastrointestinal (GI) tract over an extended period of time (b) (4) to produce an extended duration of action. Xartemis XR is a bimodal-biphasic, (b) (4) release (b) (4) formulation that contains (b) (4)% oxycodone (b) (4)% acetaminophen (b) (4) (w/w) in the IR component designed to provide rapid analgesic onset, and (b) (4)% oxycodone (b) (4)% acetaminophen (b) (4) in the ER component with the objective to provide an extended duration of analgesia.

As with other oral Schedule II opioids, Xartemis XR has the risk of adverse outcomes (e.g., respiratory depression, death) due to abuse and misuse, tolerance, and dependence (See Section 3.2 for further details).

If approved, it will be the first extended-release oxycodone/acetaminophen combination product, as well as the first extended-release opioid product to carry an acute pain indication. (b) (4)

Percocet, which is currently available in the following oxycodone/acetaminophen strength combinations: 2.5 mg/325 mg, 5 mg/325 mg, 7.5 mg/ 325 mg, 10 mg/ 325 mg, 7.5 mg/500 mg, and 10 mg/650 mg. The only product characteristic difference between the immediate-release product and Xartemis XR is duration of action. Percocet is not marketed under a REMS.

1.2 REGULATORY HISTORY

On January 7, 2013, the Agency informed the Sponsor in a pre-NDA meeting that Xartemis XR would be included in the ER/LA REMS program, secondary to the proposed properties of their tablet.

On May 28, 2013, the Sponsor submitted the NDA for Xartemis XR as a 505(b)(2) application, which utilized the safety and efficacy of Roxicodone (oxycodone, NDA 021-011) and Ultracet (tramadol HCl/acetaminophen, NDA 021-123). The NDA submission also included a proposed REMS, which integrated Xartemis XR into the approved ER/LA Opioid Analgesics REMS (ER/LA REMS).

DRISK conducted a preliminary review of the proposed REMS, dated October 17, 2013. Initial comments on the proposed REMS were communicated to the Sponsor on October 18, 2013, to which the Applicant responded on October 25, 2013.

Upon further internal discussion, DAAAP determined the ER/LA REMS was not appropriate for Xartemis XR due to its proposed indication for acute pain (see Section 3 for further details). Inclusion of a product which has an acute pain indication in the ER/LA REMS would undermine the following key educational message of the ER/LA REMS: ER/LA products indicated for chronic use could cause fatal outcomes if used acutely. Furthermore, (b) (4)

do not apply to Xartemis XR, because the epidemiologic studies require data from chronic use of the included medications. Additionally, the inclusion of Xartemis XR in this data set may skew the results, as it may be difficult, depending on data source, to detect or exclude it from the other products. However, since this is an extended-release formulation, the labeling for Xartemis XR will closely reflect that of the other extended-release opioid medications.

DAAAP presented the aforementioned recommendation to the management of Office of Drug Evaluation (ODE) II in late-October 2013, to the ER/LA REMS Implementation team on November 5, 2013, and to the Opioid Task force on November 6, 2013. The teams were in agreement with DAAAPs recommendation.

DRISK and DAAAP determined that a REMS for Xartemis XR is not required and presented the recommendation to the REMS Oversight Committee on November 13, 2013, where the ROC members concurred.

On November 14, 2013, DAAAP informed the Sponsor that a REMS was not required to ensure the benefits outweighed the risks for Xartemis XR at a Type B meeting for another product (hydrocodone/acetaminophen) in development by the Sponsor.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Mallinckrodt, Inc. Amended Proposed REMS for Xartemis XR (oxycodone HCl/acetaminophen), received on October 25, 2013. (Sequence No. 0011)
- Mallinckrodt, Inc. Proposed REMS for Xartemis XR (oxycodone HCl/acetaminophen), received on May 28, 2013. (Sequence No. 0000)
- D. Smith. DRISK Interim Comments Set #1 for Xartemis XR. October 17, 2013.

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- 11/7/2013 Enhanced Package Insert Labeling (Developed by Deputy Division Director)
- 11/7/2013 Cross-Discipline Team Leader (CDTL) Review

3 RESULTS OF REVIEW OF PROPOSED XARTEMIS XR RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The phase 3 program for Xartemis XR was supported by 1 efficacy study (Study 0182) and 1 safety study (Study 0181).

- Study 0182: a double-blind, randomized, placebo-controlled parallel-group efficacy study, enrolled 329 subjects at 5 sites. The study included a 48-hour blinded dosing phase followed by an optional 14-day open-label extension (OLE). The blinded dosing phase of the study was designed to evaluate the safety and efficacy of Xartemis XR versus placebo. Study subjects with acute postoperative pain of moderate to severe intensity (a score of at least 4 on an 11 point numerical rating scale) following unilateral bunionectomy surgery were randomized and stayed at the study site for the duration of the blinded dosing phase. Rescue medication was provided and could be taken as needed up to six times per day (ibuprofen 400 mg).
- Study 0181: a multicenter, open-label safety study of osteoarthritis and chronic lower back pain subjects, enrolled 376 subjects at 38 sites. Subjects included those who were transitioning from Step 1 of the World Health Organization (WHO) pain scale (nonsteroidal anti-inflammatory drugs [NSAIDs] and other nonopioid medications to control pain) to Step 2 of the WHO pain scale (eg, needing to escalate to opioid combinations or lower-dose opioids plus NSAIDs to control pain). Subjects were treated with 2 tablets of Xartemis XR every 12 hours for up to 35 days. The purpose of this study was to collect safety data on the short-term use of Xartemis XR in populations who frequently use low-dose opioids for short periods of time, similar to the treatment of acute pain, and to obtain supportive efficacy data.

Study 0182 showed statistically significantly less pain over 48 hours [(primary endpoint, greater mean summed pain intensity difference over the first 48 hours (SPID₄₈)] for Xartemis XR versus placebo ($P < 0.001$), indicating significant pain relief throughout the double-blind dosing phase. These efficacy findings support approval for the proposed indication.

3.2 SAFETY CONCERNS

Treatment emergent adverse events (TEAEs) that occurred more frequently in the Xartemis XR treatment group (pooled, greater than 2%) were gastrointestinal disorders (38.1%), nervous system disorders (27.3%), and skin and subcutaneous tissue disorders (10.2%) with pruritus comprising the majority of these cases (9 out of 19).

There were a total of six non-fatal serious adverse events (SAEs); five of which were in the treatment arm of the study. Only two of the five cases [abdominal pain requiring hospitalization and gastroesophageal reflux disease (GERD)] were causally related to Xartemis XR. Additionally, there were two deaths reported in the open-label Phase 3 study amongst patients receiving Xartemis XR; however, DAAAP's assessment indicates that both appear unlikely to be related to study drug. Overall there were no new or unexpected safety signals for Xartemis XR that have not been seen with other single ingredient opioids (immediate and extended-release) or opioid/acetaminophen combination products.

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE SPONSOR

The sponsor submitted a REMS which integrated their product specific information into the existing ER/LA REMS, due to the extended-release properties of their product and upon the advice of the Agency in a pre-NDA meeting.

The REMS for ER/LA opioid analgesics includes brand name and generic products formulated with the active ingredients: fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone and tapentadol. Currently available ER/LA opioid analgesics are approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The sponsor has not proposed any additional risk mitigation strategies.

4 DRISK'S EVALUATION OF THE NEED FOR A REMS FOR XARTEMIS XR

All opioid formulations have the potential for misuse, abuse, overdose and death. The Agency believes that the currently approved ER/LA opioids pose a higher risk for the aforementioned safety concerns than immediate-release opioid formulations because they include dosage forms that contain more opioid per tablet, capsule or patch and either stay in the body longer or are released into the body over longer periods of time. Additionally, when the extended-release features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an immediate-release manner, potentially resulting in overdose or death. However, the dose for Xartemis XR is equivalent to that of an immediate-release oxycodone/acetaminophen (Percocet) tablet; the strength falls into the middle of the dose range of that product line (See Section 1.1), thus manipulation of the extended release properties of Xartemis XR would be comparable to taking a Percocet with the same strengths of the active ingredients. Therefore, the extent of risk for the adverse consequences associated with manipulation of Xartemis XR is not equivalent to the risk for products currently covered under the ER/LA REMS. Additionally, this product has a dosing limit due to the acetaminophen component, therefore it also differs from the other extended-release opioid products as there is a dosing ceiling with this product.

If approved, Xartemis XR will represent this first extended-release opioid tablet, (single entity or combination) with an acute pain indication, and the inclusion of a product which has an acute pain indication in the ER/LA REMS would undermine a key educational

message of the ER/LA REMS; ER/LA products indicated for chronic use could cause fatal outcomes if used acutely.

However, Xartemis XR will have a label more consistent with the ER/LA opioid analgesics. This includes revised and enhanced labeling regarding indication, abuse, misuse, and diversion that will be included for all the ER/LA products under the ongoing Safety Labeling Changes (letter sent to sponsors September 10, 2013). Furthermore, Xartemis XR will include a Medication Guide, which will be reviewed by Office of Medical Policy/Patient Labeling Team under a separate cover. This enhanced labeling potentially provides greater risk mitigation than the current IR oxycodone/acetaminophen product labeling and is sufficient to mitigate the risks surrounding labeled use of this product at this time.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Xartemis XR. The safety profile for Xartemis XR is consistent with currently approved IR formulations of oxycodone/acetaminophen. There were no new or unique safety concerns associated with Xartemis XR identified in the pivotal trials. Furthermore, IR oxycodone/acetaminophen do not currently have an approved REMS. Therefore, a REMS is not recommended for Xartemis XR.

Should DAAAP raise further concerns with the risks outlined above or identify additional risks associated with Xartemis XR warranting more extensive risk mitigation or a formal REMS, please send a consult to DRISK.

This memo serves to close the existing consult request for Xartemis XR under NDA 204-031. Please notify DRISK if you have any questions.

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

/s/

JAMIE C WILKINS PARKER
01/28/2014

CLAUDIA B MANZO
01/30/2014
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**

**Interim Comments on Risk Evaluation and Mitigation Strategy (REMS)
Set # 1**

Date: October 17, 2013

Reviewer(s): Danielle J. Smith, Pharm.D, MS
Division of Risk Management (DRISK)

Acting Team Leader: Kimberly Lehrfeld, Pharm.D, BCPS
DRISK

Division Director: Claudia Manzo, Pharm.D
DRISK

Drug Name(s): Xartemis XR (oxycodone and acetaminophen)

Therapeutic Class: Opioid Agonist

Dosage and Route: 7.5 mg oxycodone hydrochloride and 325 mg
acetaminophen oral tablets

Application Type/Number: NDA 204-031

Submission Number: 0000

Applicant/sponsor: Mallinckrodt, Inc.

OSE RCM #: 2013-1270

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

CONTENTS

1	INTRODUCTION	1
1.1	Background	1
2	MATERIALS REVIEWED	1
2.1	Submissions.....	1
2.2	Other Materials Informing Our Review	1
3	SUMMARY OF APPLICANT’S PROPOSED REMS	1
3.1	Goals.....	1
3.2	REMS Elements	1
3.3	REMS Assessment Plan.....	5
4	RECOMMENDATIONS FOR THE REVIEW DIVISION.....	5
5	COMMENTS FOR THE APPLICANT	5
5.1	REMS Document	5
5.2	FDA Blueprint.....	5
5.3	ER/LA Opioid Analgesics REMS Website.....	5
5.4	General Comments.....	6
6	REMS SUPPORTING DOCUMENT	6
	ATTACHMENTS.....	6

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) review of the Xartemis XR (oxycodone hydrochloride and acetaminophen extended-release) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 204-031, submitted by Mallinckrodt, Inc. on May 28, 2013 (Sequence No. 0000).

1.1 BACKGROUND

Xartemis XR (oxycodone and acetaminophen), a combination product, is proposed by the Applicant for the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. Oxycodone is an opioid agonist and is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. Acetaminophen is a non-opiate, non-salicylate analgesic, and antipyretic. The site and mechanism for the analgesic effect of acetaminophen has not been determined.

Xartemis XR is an extended-release tablet for twice daily oral administration containing both immediate- and extended-release components. Xartemis XR is formulated to immediately release a portion of its oxycodone and acetaminophen doses. It is available as an extended-release tablet containing 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen.

Xartemis XR is an extended-release Schedule II opioid analgesic with no abuse-deterrent properties. It poses the same risks of abuse/misuse, tolerance, dependence and withdrawal syndrome as other extended-release opioid products. 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 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 204-031 for the proposed ER/LA Opioid Analgesics REMS:

- 05/28/2013 Proposed REMS (Sequence No. 0000)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- ER/LA Opioid Analgesic REMS, approved on July 9, 2012; modified on August 24, 2012, August 28, 2012, and April 15, 2013

3 SUMMARY OF APPLICANT'S PROPOSED REMS

3.1 GOALS

There are no recommendations for revisions to the goals of the REMS.

3.2 REMS ELEMENTS

3.2.1 Medication Guide

The Division of Medical Policy Programs, Patient Labeling Team will evaluate the Sponsor's proposed Medication Guide and provide a separate review to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

3.2.2 Elements to Assure Safe Use

3.2.2.1 Training will be made available to healthcare providers who prescriber ER/LA opioid analgesics

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.3 REMS ASSESSMENT PLAN

There are no recommendations for revisions to REMS assessment plan.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Xartemis XR proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal. Appended to this review is the REMS proposal and REMS materials (Patient Counseling Document, FDA Blueprint, Prescriber Letters 1, 2, and 3, Organization Letters 1 and 2, and the ER/LA Opioid Analgesic REMS website including our track changes (see Attachments). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE APPLICANT

46 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DANIELLE SMITH
10/17/2013

KIMBERLY LEHRFELD
10/17/2013