CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum - Correction

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

NDA/BLA #s:	205777
Products:	Targiniq ER (oxycodone/naloxone extended-release tablets)
SPONSOR:	Purdue Pharma
FROM:	Judith A. Racoosin, MD, MPH
DATE:	July 23, 2014

In a REMS memorandum dated June 24, 2014, I stated the following regarding the extended release and long-acting (ER/LA) opioid analgesic REMS that Targiniq ER was joining, "The elements of the REMS will be a Medication Guide, Elements to Assure Safe Use, an implementation plan, and a timetable for submission of assessments of the REMS."

My inclusion of an implementation plan as an element of the ER/LA opioid analgesic REMS was incorrect. As is stated in the original approval letter for this REMS, dated July 9, 2012, it consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

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/s/

JUDITH A RACOOSIN
07/23/2014

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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 22, 2014
Reviewer(s):	Kim Lehrfeld, Pharm. D., BCPS, Risk Management Analyst Division of Risk Management Joan Blair, R.N., M.P.H., Health Communications Analyst Division of Risk Management
Team Leader:	Kim Lehrfeld, Pharm. D., BCPS Division of Risk Management
Acting Deputy Director:	Reema Mehta, Pharm.D., MPH Division of Risk Management
Drug Name(s):	Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) tablets
Therapeutic Class:	Opioid analgesic
Dosage and Route:	10mg/5mg, 20mg/10mg, 40mg/20mg extended-release tablet
Application Type/Number:	NDA 205777
Submission Number:	Sequence No. 0038
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2013-2371

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

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EXECUTIVE SUMMARY

The purpose of this review is to document Division of Risk Management's (DRISK's) evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) extended release tablets (NDA 205777) and evaluation of the Purdue's amended REMS submission, received July 21, 2014 (Sequence No.0038).

The Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS was originally approved on July 9, 2012 to address the risks of misuse, abuse, overdose and death and REMS modifications were approved August 28, 2012, and April 15, 2013.

As an extended-release Schedule II opioid analgesic, Targiniq ER poses a risk of abuse/misuse, tolerance, dependence and withdrawal syndrome. Therefore, it was expected that Targiniq ER would be incorporated into the ER/LA Opioid Analgesics REMS. OSE, DRISK recommends approval of the ER/LA Opioid Analgesics REMS to incorporate Targiniq ER.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 205777, submitted by Purdue, Inc. on September 23, 2013 (Sequence No.0000) and amended on December 9, 2013 (Sequence No.0011) and July 21, 2014 (Sequence No. 0038). The purpose of this review is to document DRISK's evaluation of the need for a REMS for Targiniq and evaluation of the Sponsor's amended final REMS submission.

1.1 PRODUCT BACKGROUND

Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride), is a 12-hour extended-release formulation of oxycodone and naloxone. If approved, it will be available as 10mg/5mg, 20mg/10mg, and 40mg/20 mg oral extended-release tablets.

The active ingredient, oxycodone, is an opioid agonist which is proposed by the Sponsor for the management of (b) (4) pain (b) (4), around-the-clock (b) (4)

This product also contains an opioid antagonist (naloxone) which is only active if the product is not used as intended (i.e. manipulated or at doses above the recommended dose). Naloxone is intended as an abuse deterrent since it will be active if the product is manipulated and injected intravenously or inhaled nasally. Targiniq ER was found to be resistant to many forms of chemical manipulation commonly employed by substance abusers to differentially extract oxycodone or inactivate naloxone. The data from the clinical abuse potential studies indicate that Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal, intravenous, and oral routes of administration. However, abuse of Targiniq ER by these routes is still possible.

In addition, at dosed greater than 80mg/40mg per day (40mg/20mg every 12 hours), there is the potential for symptoms of opioid withdrawal or decreased analgesia due to some absorption of the naloxone component which is not observed at lower doses. Therefore, there will be a limitation of use in the Dosage and Administration Section of the PI stating the "maximum total daily dose of Targiniq ER should not exceed 80 mg/40 mg (40 mg/20 mg q12h) because higher doses may be associated with symptoms of opioid withdrawal or decreased analgesia."

Finally, like other extended-release opioid products, Targiniq ER poses a risk of abuse/misuse, tolerance, dependence and withdrawal syndrome. 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.

1.2 REGULATORY HISTORY

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

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

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

On September 23, 2013, Purdue submitted NDA 205777 for Targiniq ER as a 505(b)(2) application (Seq. No 000), relying on prior findings of safety and efficacy for approved NDA products, OxyContin (oxycodone extended release NDA 022272 and its predecessor NDA 020553) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan since Narcan is not available on the market). In the NDA submission, the Sponsor included a REMS proposal.

[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.

On November 27, 2013, Purdue informed FDA, via email, that the REMS submitted as part of the original NDA on September 23, 2013, did not include the Targiniq-specific information for the ERLA REMS blueprint. Therefore they would be making an additional submission to their application with a revised REMS. This submission was received on December 9, 2013 (Seq. No 0011).

On June 30, 2014, the Agency approved a Prior Approval Supplement (PAS) for the manufacturing of a new 7.5 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal system (NDA 21306). The supplement affected the FDA Blueprint, which was revised to include the new dosage strength. This revision must be incorporated into the ERLA REMS for Targiniq. Therefore, on July 1, 2014, FDA requested Purdue submit revised REMS materials which incorporates the new Butrans strength.

On July 21, 2014, the Sponsor submitted a REMS amendment (Sequence No. XXX), which is the focus of this review.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following submissions, listed by date received, were reviewed from NDA 205777 for the proposed ER/LA Opioid Analgesics REMS:

- 9/23/2013 Proposed REMS (Sequence No. 0000)
    - 12/09/2013: Amendment 1 (Sequence No. 0011)
    - 7/21/2014: Amendment 2 (Sequence No. 0038)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- DAAAP Cross-Discipline Team Leader Review, E. Fields, July 14, 2014
- DAAAP Clinical Review, E. Kilgore, June 19, 2014
- Clinical Pharmacology NDA review, S Nallani, June 18, 2014
- Pharmacology /Toxicology NDA review, B Hayes, June 24, 2014
- ER/LA Opioid Analgesic REMS, approved on July 9, 2012; modified on July 25, 2013

3 RESULTS OF REVIEW OF PROPOSED ER/LA OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

3.1.1 Efficacy

The Sponsor demonstrated the efficacy of Targiniq ER, as required by the Agency, in a single adequate and well-controlled clinical trial. The Phase 3 randomized, double-blind, placebo-controlled, parallel-arm enriched design study was conducted in subjects with chronic low back pain who required around the clock opioids in a range of 20 mg to 160

mg morphine equivalents. A total of 1095 patients with uncontrolled, moderate to severe chronic low back pain entered an open-label, dose-titration period for up to four weeks. Fifty-five percent (55%) of patients who entered the open-label titration period achieved adequate analgesia and tolerability on Targiniq ER and were then randomized to their final titrated dose of Targiniq ER (n=298) or matching placebo (n=302) for 12 weeks of double-blind treatment.

The primary efficacy endpoint was the difference in mean average pain in the last 24 hours score between placebo and Targiniq ER at week 12. The difference in primary efficacy endpoint between Targiniq ER and placebo was statistically significant. The secondary endpoints (Medical Outcomes Survey (MOS) Sleep Scale and Patient Global Impression of Change (PGIC)) supported the primary endpoint results.

3.1.2 Safety Concerns

The safety data provided by the Sponsor demonstrated that during the development of Targiniq ER the safety profile was consistent with other extended-release opioid analgesics when used as the proposed labeling describes in patients with chronic pain who require treatment with an around-the-clock opioid analgesic. There were no deaths attributable to Targiniq ER and no unexpected or unusual adverse events of special interest were identified.

Due to the inclusion of naloxone in Targiniq ER, drug withdrawal syndrome was looked at closely by the clinical reviewer, Dr. Kilgore. She notes the following in her review:

> In the investigator-identified cases of opioid withdrawal, there was a slightly higher incidence of "Drug withdrawal syndrome" in the Targiniq ER treated subjects in the double-blind period compared to placebo being 3% and 2%, respectively. When the adjudicated cases of opioid withdrawal are included, there are 4% of Targiniq ER treated subjects with possible opioid withdrawal compared with 2% in placebo. It is not definitive, however, whether the increased incidence of withdrawal in Targiniq ER-treated subjects is due to the inclusion of naloxone. Most cases identified as drug withdrawal syndrome or possible drug withdrawal (determined by an independent Adjudication Committee) were mild to moderate in severity, resolved spontaneously, and did not require intervention other than dose adjustment or discontinuation of Targiniq ER.

However, based on an analysis of pharmacokinetic data and a simulation conducted by the clinical pharmacology reviewer (Nallani, Srikanth C, June 18, 2014), daily doses above 80/40 mg (40/20 mg twice daily) may result in exposure to naloxone that can result in opioid withdrawal symptoms. As a result, Targiniq ER will be approved with a maximum daily dose of 80/40 mg (40/20 mg twice daily). In contrast, the approved extended-release oxycodone product (OxyContin) has no upper dosage limit and can be titrated to effect and tolerability.

The following proposed PI text, in addition to text within the ER/LA REMS Blueprint (see Section 3 of this review), adequately addresses the potential risk of opioid withdrawal symptoms due to naloxone component of Targiniq ER.

- INDICATION AND USAGE

Limitations of Use

The maximum total daily dose of TARGINIQ ER should not exceed 80 mg/40 mg (40 mg/20 mg q12h) because higher doses may be associated with symptoms of opioid withdrawal or decreased analgesia *[see Warnings and Precautions 5.11]*.

- DOSAGE AND ADMINISTRATION

2.2 TITRATION AND MAINTENANCE OF THERAPY

The highest total daily dose of TARGINIQ ER studied in the main clinical program is 80 mg/40 mg (40 mg/20 mg twice daily). Total daily doses above 80 mg/40 mg have not been studied sufficiently to ensure patient safety and may be associated with symptoms of opioid withdrawal or decreased analgesia.

- WARNINGS AND PRECAUTIONS

5.11 AVOIDANCE OF WITHDRAWAL

Symptoms of opioid withdrawal occurred in some patients in clinical trials *[see Adverse Reactions (6.1)]*. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Monitor patients for symptoms of opioid withdrawal. In opioid tolerant patients, if symptoms of opioid withdrawal occur following conversion to TARGINIQ ER or following dose escalation, consider lowering the dose to determine whether symptoms are reduced.

- ADVERSE REACTIONS

6.1 CLINICAL TRIAL EXPERIENCE

Table 4. Incidence of Treatment-Emergent Adverse Reactions Reported in ≥ 2% of Subjects Taking TARGINIQ ER: Safety Population (Open-label Titration Period) and Randomized Safety Population (Double-blind Period)

	Open-Label Period	Double-blind Period	
MedDRA System Organ Class Preferred Term	**TARGINIQ ER (N=1095) (%)**	**Placebo (N=302) (%)**	**TARGINIQ ER (N=298) (%)**
Nausea	7	5	8
Headache	4	3	3
Constipation	3	1	3
Vomiting	2	2	5
Abdominal pain	3	2	3
Anxiety	1	(b) (4)	3
***Drug withdrawal syndrome (bold added by reviewer for emphasis)**	1	2	3
Insomnia	1	1	2
(b) (4)			
Back pain	(b) (4)	1	3

***Percentages in the table are based on adverse reaction reports of Drug Withdrawal Syndrome in the key efficacy and safety study. In addition to the adverse reaction reports, an independent Adjudication Committee identified additional subjects with possible drug withdrawal syndrome, resulting in a total (adverse reactions plus adjudicated cases) of 2% of subjects in the Open-label Period, and in the double-blind period 4% of subjects treated with TARGINIQ ER and 2% treated with placebo. (bold added by reviewer for emphasis)**

3.2 DRISK RATIONALE FOR A REMS FOR TARGINIQ ER

All opioid formulations have the potential for misuse, abuse, overdose and death. The Agency believes that ER/LA opioids pose a higher risk for the aforementioned safety concerns than immediate-release opioid formulations because they contain more opioid per tablet, capsule or patch and 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. Therefore, the ER/LA Opioid Analgesic REMS was developed and approved to mitigate these risks. Since Targiniq ER contains oxycodone in doses which, when manipulated and taken orally, could potentially result in overdose or death, if approved it is appropriate for it to join the single, shared system ER/LA REMS.

3.3 REVIEW OF PROPOSED REMS FOR TARGINIQ ER

The focus of the review of the proposed REMS for Targiniq ER was to incorporate Targiniq ER into the approved ER/LA REMS. Purdue made the following revisions to the approved ER/LA REMS.

FDA Blueprint

(b) (4)

- Incorporated the following product-specific information for Targiniq ER:

Targiniq ER	▪ Oxycodone Hydrochloride / Naloxone Hydrochloride ▪ Extended-release tablets, 10/5 mg, 20/10 mg, and 40/20 mg
Dosing Interval	Every 12 hours
Key Instructions	▪ (b) (4)
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase (b) (4). ▪ CYP3A4 inducers may decrease (b) (4)
Use in Opioid-Tolerant Patients	(b) (4)
Product-Specific Safety	▪ (b) (4)
Relative Potency To Oral	(b) (4)

4 DISCUSSION

DAAAP recommended approval of Targiniq ER based on demonstrated efficacy and a safety profile which is consistent with other ER opioid analgesics.

An additional potential safety issue of concern with Targiniq is the potential for withdrawal at high doses due to the naloxone component. Based on an analysis of pharmacokinetic data and a simulation conducted by the clinical pharmacology reviewer, doses above this may result in exposure to naloxone that can result in opioid withdrawal symptoms. As a result, Targiniq ER will be approved with a maximum daily dose of 80/40 mg (40/20 mg twice daily). The PI will contain language in multiple sections

(Indication and Usage, Dosage and Administration, [redacted](b) (4)) describing the potential risk of withdrawal at higher than recommended doses.

The DAAAP clinical reviewer, Dr. Elisabeth Kilgore summarized the Risk/Benefit of Targiniq ER in her clinical review (June 24, 2014) as follows:

> As an extended-release Schedule II opioid analgesic, the risks (including overdose, misuse and abuse) associated with this product appear similar to other opioids in this class. These risks, however, appear to be manageable with the labeling and REMS and should not preclude approval. The presence of abuse deterrent features may provide an incremental improvement regarding abuse liability.

DRISK agrees with Dr. Kilgore's assessment that Targiniq ER poses a risk of abuse/misuse, tolerance, dependence and withdrawal syndrome similar to other extended-release opioid products. If approved, Targiniq ER will be incorporated into the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS.

DRISK agrees with the addition of Targiniq ER to the approved ER/LA Opioid Analgesics REMS.

5 CONCLUSION

In conclusion, the amended REMS the ER/LA Opioid Analgesic REMS to incorporate the approval for Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride), received September 23, 2013, and amended on December 9, 2013 and July 21, 2014, contains the appropriate and agreed upon revisions on the REMS components as stipulated by the Agency. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the ER/LA Opioid Analgesics REMS in achieving the goals. The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on July 9, 2012.

Therefore, the modified ER/LA Opioid Analgesics REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

The above revisions will be incorporated into the current REMS modification to align the ERLA REMS with the approved Safety Label Changes (SLC) that is under review by the agency.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the REMS Modification for ER/LA Opioid Analgesic REMS July 21, 2014 and appended to this review.

The Approval Letter should reference the REMS assessment plan included with the July 9, 2012 REMS approval.

ATTACHMENTS

Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS

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/s/

KIMBERLY LEHRFELD
07/22/2014

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07/22/2014

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 Rheumatology Products

NDA/BLA #s:	205777
Products:	Targiniq ER (oxycodone/naloxone extended-release tablets)
SPONSOR:	Purdue Pharma
FROM:	Judith A. Racoosin, MD, MPH
DATE:	June 23, 2014

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 death, overdose and addiction. 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.[1] 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

[1] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf

prescribed and used safely among the intended population, FDA has determined that a REMS is necessary to address the issues of unintentional overdose, addiction, 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.[2] In year 2009, an estimated (b) (4) unique patients received a dispensed prescription for an ER/LA opioid analgesic product from outpatient retail pharmacies.[3]

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.[4]

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.[5] 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.[6]

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[2] Nelson, R. Lancet 362(9390); 1129, 2003.
[3] SDI, Total Patient Tracker. Year 2009, Extracted, June 2010.
[4] SDI, Physician Drug and Diagnosis Audit, Year 2009, Extracted June 2010
[5] Balch RJ, et al. Extended-release morphine sulfate in treatment of severe acute and chronic pain. J*ournal of Pain Research* 2010:3 191–200.
[6] SDI, Vector One®: National. Years 2000 – 2009, Extracted June 2010.

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 deaths, unintentional overdose, and addiction, 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 such as oxycodone, morphine, fentanyl, buprenorphine, methadone, and hydromorphone; none of these active drug substances are new molecular entities. Oxycodone, the extended release opioid in Targiniq ER, is also not a new molecular entity.

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, an implementation plan, and a timetable for submission of assessments of the REMS.

The ER/LA opioid analgesic single shared system REMS was approved July 8, 2012. Upon approval, Targiniq ER will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
06/24/2014

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan Blair, Health Communications Analyst, DRISK

From: Eunice Chung-Davies, Regulatory Review Officer

CC: Sam Skariah, Team Leader
Vaishali Jarral, RPM, OSE
Kimberly Lehrfeld, Team Leader, DRISK
Jamie Wilkins-Parker, Senior Risk Management Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: June 26, 2014

Re: Targiniq™ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII
(b) (5)

Materials Reviewed

(b) (5)

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/s/

BRENDA V BORDERS-HEMPHILL
06/26/2014

IRENE Z CHAN
06/26/2014

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan Blair, Health Communications Analyst, DRISK

From: Eunice Chung-Davies, Regulatory Review Officer

CC: Shenee' Toombs, Regulatory Review Officer
Sam Skariah, Team Leader
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Kimberly Lehrfeld, Team Leader, DRISK
Jamie Wilkins-Parker, Senior Risk Management Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: March 27, 2014

Re: Extended-Release/Long-Acting (ER/LA) Opioid Products
Comments on draft SSS Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed SSS REMS materials for ER/LA opioid products

- Healthcare Provider (HCP) REMS Materials:

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/s/

EUNICE H CHUNG-DAVIES
04/07/2014