

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202880Orig1s000

**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: September 23, 2013

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Drug Name(s): Zohydro ER (hydrocodone bitartrate)

Therapeutic Class: Opioid analgesic

Dosage and Route: 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules

Application Type/Number: NDA 202-880

Submission Number: Sequence No. 0023

Applicant/sponsor: Zogenix, Inc.

OSE RCM #: 2012-1666

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

CONTENTS

1	INTRODUCTION	1
1.1	Background	1
1.2	Safety Concerns	2
1.3	Regulatory History	2
2	MATERIALS REVIEWED	5
2.1	Data and Information Sources	5
2.2	Other Materials Informing our review	5
3	RESULTS OF REVIEW OF PROPOSED ER/LA OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY MODIFICATION.....	5
4	DISCUSSION.....	6
5	CONCLUSION	6
6	RECOMMENDATIONS.....	7
	ATTACHMENTS.....	7

EXECUTIVE SUMMARY

This is a review of Zogenix's proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Zohydro ER (hydrocodone bitartrate ER capsules) (NDA202-880) initially received May 01, 2012 (Sequence No. 0000) and amended on January 11, 2013 (Sequence No. 0016), May 30, 2013 (Sequence No. 0022), and July 30, 2013 (Sequence No. 0023).

The 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 on August 24, 2012, August 28, 2012, and April 15, 2013.

As an extended-release Schedule II opioid analgesic, Zohydro ER poses the same risks of abuse/misuse, tolerance, dependence and withdrawal syndrome as other extended-release opioid products. Therefore, it was expected that Zohydro ER would be incorporated into the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS. OSE, DRISK recommends approval of the ER/LA Opioid Analgesic REMS to incorporate the approval for Zohydro ER.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the Zohydro ER (hydrocodone bitartrate) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 202-880, submitted by Zogenix, Inc. on May 01, 2012 (Sequence No. 0000) and amended on January 11, 2013 (Sequence No. 0016), May 30, 2013 (Sequence No. 0022), and July 30, 2013 (Sequence No. 0023).

1.1 BACKGROUND

Zohydro ER (hydrocodone bitartrate), an opioid agonist, is proposed by the Sponsor for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Sponsor's product is a 12-hour extended-release formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS[®]) drug delivery technology. It is available as 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules.

Hydrocodone is currently available only as a combination product with non-narcotic analgesics such as ibuprofen, acetaminophen, and aspirin. According to the Controlled Substance Act, Schedule III controls apply to hydrocodone combination products containing no more than 300 mg per 100 mL or not more than 15 mg of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. All currently approved combination hydrocodone products fall under Schedule III. However, Zohydro ER, as a single-entity product, would be regulated under Schedule II.

Zohydro ER 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.

1.2 SAFETY CONCERNS

The Sponsor has demonstrated the efficacy of Zohydro ER, as required by the Agency, in a single adequate and well-controlled clinical trial in subjects with chronic low back pain. The safety data provided by the Sponsor demonstrated that during the development of Zohydro ER the safety profile was consistent with other extended-release opioid analgesics when used as labeled in patients with chronic pain who require treatment with an around-the-clock opioid analgesic. No new or unexpected safety signals were identified during review of this NDA.

As a Schedule II opioid analgesic, it is not unexpected that events of misuse, abuse, and diversion would be reported during the clinical trials of Zohydro ER. The Sponsor reported 92 diversion-related adverse events in studies 801 and 802. Examples of abuse included tampering with the urine drug screen sample, and tampering with the rescue medication to extract hydrocodone, and obtaining prescriptions from more than one prescriber for hydrocodone/acetaminophen. Hydrocodone is a Schedule II opioid analgesic with abuse liability similar to other drugs its class. In fact, additional in vivo human abuse liability studies were not required for this application since the abuse liability of this drug substance is well known, and the Sponsor has made no claims that Zohydro ER is an abuse deterrent formulation.

1.3 REGULATORY HISTORY

In February 2009, the FDA notified Sponsors of ER/LA opioid analgesics that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. The Sponsors were notified that the REMS would include ER/LA opioid analgesic NDA and ANDA products formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

On May 1, 2012, Zogenix submitted NDA 202-880 for Zohydro ER as a 505(b)2 application, relying on prior findings of safety and efficacy for Vicoprofen[®] (hydrocodone/ibuprofen; NDA 20-716). In the NDA submission, the Sponsor included a REMS proposal, which was an obsolete version of the proposed SSS REMS for ER/LA opioid analgesics.

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

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.

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 December 7, 2012, the Agency held an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting, in which the committee was asked to determine whether the benefit-risk assessment of Zohydro ER favors its approval for marketing. The committee voted 11-2, with one abstention, against the approval of Zohydro ER. During the AADPAC meeting, the committee was also asked to discuss whether the data supported the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS. The Sponsor provided a summary of additional proposed risk mitigation activities to supplement the ER/LA Opioid Analgesics REMS, which included the following:

1. Commercialize Zohydro ER responsibly
 - a. Focused prescriber target audience – Practitioners who are experienced ER/LA opioid prescribers for chronic pain patients
 - b. Incentivize education and safe use
 - c. Introduce Zohydro ER with a limited top dose strength
2. Augment the ER/LA REMS with their voluntary Zohydro ER Safe-Use initiative that is designed to
 - a. Increase and improve participation in training programs and monitor effectiveness
 - b. Uphold safe use among patients
 - c. Implement rigorous utilization surveillance systems
 - d. Take corrective actions if issues are detected
3. Share learning and best practices
 - a. Provide practical solutions for home safekeeping for patients
 - b. Improve prescriber training participation and effectiveness

c. Expand training across healthcare stakeholders including pharmacists

These voluntary risk mitigation efforts were not submitted to the NDA for Agency review.

The committee felt that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for ER/LA opioids in general, including Zohydro ER. They stated there is a need for additional postmarketing risk mitigation requirements beyond the current REMS for the entire class.

On December 14, 2012, OND informed the Sponsor to submit a revised REMS that is in accordance with the currently approved version (as of August 28, 2012) of the ER/LA REMS and includes all necessary drug-specific information for Zohydro ER. On January 11, 2013, the Sponsor submitted a REMS Amendment to their application. On February 22, 2013, the Sponsor was sent DRISK interim comments set #1.

On January 31, 2013, DAAAP's Cross-Discipline Team Leader's (CDTL) review of Zohydro ER recommended approval of Zohydro ER (E. Fields Jan 31, 2012). The following summarizes the rationale for approval:

The Applicant has demonstrated the efficacy of Zohydro ER, as required by the Agency, in a single adequate and well-controlled clinical trial in subjects with chronic low back pain, and has shown that the safety profile appears similar to other approved extended-release opioid analgesics.

It would seem that there are no issues that would preclude approval of Zohydro ER for the proposed indication, the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

Therefore, although I have concerns regarding the abuse and misuse of Zohydro ER, these concerns are similar for all of the marketed, non-abuse deterrent formulations of ER/LA opioid analgesics. Until the Agency develops a regulation or policy that requires this class of drug have abuse deterrent or tamper resistant properties, the only viable regulatory option at this time is to approve Zohydro ER for the proposed indication.

On May 30, 2013, the Sponsor amended the proposed REMS (Sequence No. 0022).

On July 23, 2013, the Sponsor was sent a comment to make text visible in the Zohydro ER product-specific information of the FDA Blueprint.

On July 25, 2013, the Agency approved a Prior Approval Supplement (PAS) for the manufacturing of a new 15 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal system. The supplement affected the FDA Blueprint, which was revised to include the new dosage strength. Therefore, a REMS modification to the ER/LA Opioid Analgesics REMS was necessary. The ER/LA Opioid Analgesics REMS modification was also approved at the time an intermediate dosage strength of Butrans was approved on July 25, 2013.

On July 25, 2013, Zogenix was sent DRISK interim comments set #2.

On July 30, 2013, Zogenix submitted a REMS amendment (Sequence No. 0023), 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 202-880 for the proposed ER/LA Opioid Analgesics REMS:

- 05/01/2012 Proposed REMS (Sequence No. 0000)
 - 01/11/2013: Amendment 1 (Sequence No. 0016)
 - 05/30/2013: Amendment 2 (Sequence No. 0022)
 - 07/30/2013: Amendment 3 (Sequence No. 0023)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- DAAAP Cross-Discipline Team Leader Review (dated January 31, 2013)
- ER/LA Opioid Analgesic REMS, approved on July 9, 2012; modified on July 25, 2013
- Division of Risk Management Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set #1 for Zohydro ER (dated February 20, 2013)
- Division of Risk Management Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set #2 for Zohydro ER (dated July 25, 2013)

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

The focus of the review of the proposed REMS for Zohydro was to incorporate Zohydro ER into the approved ER/LA REMS. Zogenix made the following revisions to the approved ER/LA REMS. See DRISK Interim Comments REMS Reviews dated February 20, 2013 and July 25, 2013 for details.

FDA Blueprint

- Incorporated the recently approved 15 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal System
- Incorporated the following product-specific information for Zohydro ER:

Zohydro ER	<ul style="list-style-type: none">▪ Hydrocodone Bitartrate▪ Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none">▪ Every 12 hours

Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.

Prescriber Letters 1, 2, and 3

Inclusion of Zohydro ER's established name, hydrocodone, to the listing of products subject to the ER/LA Opioid Analgesics REMS in Prescriber Letter #3.

Reviewer's Comments: The Sponsor did not propose revisions to Prescriber Letters 1 and 2 because the mailings for these letters have already occurred and will not be sent again.

ER/LA Opioid Analgesics REMS Website

Inclusion of Zohydro ER's established name, hydrocodone, to the listing of products subject to the ER/LA Opioid Analgesics REMS on the webpage entitled Selected Important Safety Information.

4 DISCUSSION

DAAAP considered current regulatory policy as it applies to the approval of ERLA opioid analgesics and recommended approval of Zohydro ER based on demonstrated efficacy and a safety profile which is consistent with other ER opioid analgesics.

As an extended-release Schedule II opioid analgesic, Zohydro ER poses the same risks of abuse/misuse, tolerance, dependence and withdrawal syndrome as other extended-release opioid products. If approved, Zohydro ER will be incorporated into the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS.

DRISK agrees with the addition of Zohydro 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 Zohydro ER (hydrocodone bitartate ER), received January 11, 2013, and amended on May 30, 2013 and July 30, 2013, 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.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the REMS Modification for ER/LA Opioid Analgesic REMS July 30, 2013 and appended to this review.

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

ATTACHMENTS

1. REMS Document
2. Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics
3. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
4. Prescriber Letter 1
5. Prescriber Letter 2
6. Prescriber Letter 3
7. Professional Organization/Licensing Board Letter 1
8. Professional Organization/Licensing Board Letter 2
9. ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com)

Initial REMS Approval: 07/2012
Most Recent Modification: 09/2013

**EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID
ANALGESICS RISK EVALUATION AND MITIGATION
STRATEGY (REMS)**

GOAL

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

I. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid analgesic prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioids are part of the ER/LA Opioid Analgesic REMS program and will be available through the ER/LA Opioid Analgesic REMS website www.ER-LA-opioidREMS.com.

B. Elements to Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.
 - a. Training will be considered “REMS-compliant training” under this REMS if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \(“FDA Blueprint”\)](#), 3) it includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
 - b. The NDA/ANDA holders of ER/LA opioid analgesic products (“NDA/ANDA holders”) will ensure that REMS-compliant training is made available to prescribers of ER/LA opioid analgesics and will achieve the following performance goals:
 - i. Not later than March 1, 2013, the first REMS-compliant training will be made available.
 - ii. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained;
 - iii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained;
 - iv. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60%

of the 320,000 active prescribers in 2011) will have been trained.

- c. The content of the REMS-compliant training will be based on the learning objectives established by the [FDA Blueprint](#). The FDA Blueprint contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics. The NDA/ANDA holders will direct providers of REMS-compliant training to the FDA Blueprint, via the REMS website (www.ER-LA-opioidREMS.com), and via its Request for Grant Applications. No less than annually, NDA/ANDA holders will direct providers of REMS-compliant training to consult the FDA Blueprint for possible revisions (e.g., changes to the drug specific information).
- d. NDA/ANDA holders will ensure that independent audits of the educational materials used by the providers of REMS-compliant training are conducted. The audits must:
 - i. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
 - ii. Evaluate:
 - 1. whether the content of the training covers all components of the [FDA Blueprint](#) approved as part of the REMS;
 - 2. whether the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - 3. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education[®] (ACCME[®]), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession.
 - iii. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals in section [B.1.b](#).
- e. To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders will make available, and then

maintain, a web site that will contain information about the REMS specified below (www.ER-LA-opioidREMS.com):

- i. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
 - ii. A copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics.
 - iii. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter) (see section B.1.f).
- f. To make prescribers aware of the existence of the REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs:
 - i. [Prescriber Letter 1](#) will be sent not later than 60 days after the initial approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\)](#).
 - ii. [Prescriber Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
 - iii. The prescribers will be identified via the DEA Registration Database.
 - iv. At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and [Prescriber Letter 3](#) will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the [Patient Counseling Document \(PCD\)](#), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.
- g. To further ensure that prescribers are aware of the existence of the ER/LA Opioid Analgesic REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail the following two letters to the professional organizations and state licensing entities listed in section [B.1.g.iii](#) with a request that the information be disseminated to their members:

- i. [Professional Organization/Licensing Board Letter 1](#) will be sent not later than 60 days after the approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\) on Extended-Release/Long-Acting Opioids](#).
- ii. [Professional Organization/Licensing Board Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
- iii. The letter and enclosures referenced above, will be sent to the following entities:
 - a) State Licensing Boards of:
 - 1) Medicine (allopathic and osteopathic)
 - 2) Nursing
 - 3) Dentistry
 - b) Associations of State Licensing Boards:
 - 1) Federation of State Medical Boards
 - 2) National Council of State Boards of Nursing
 - 3) American Association of Dental Boards
 - c) Learned Societies and Professional Associations, including, but not limited to:
 - 1) American Academy of Addiction Psychiatry
 - 2) American Academy of Family Physicians
 - 3) American Academy of Hospice and Palliative Medicine
 - 4) American Academy of Neurology
 - 5) American Academy of Nurse Practitioners
 - 6) American Academy of Nursing
 - 7) American Academy of Orofacial Pain
 - 8) American Academy of Pain Management
 - 9) American Academy of Pain Medicine
 - 10) American Academy of Physical Medicine and Rehabilitation
 - 11) American Academy of Physician Assistants

- 12) American Association of Colleges of Osteopathic Medicine
- 13) American Association of Colleges of Nursing
- 14) American Association of Poison Control Centers
- 15) American Board of Medical Specialties
- 16) American Board of Orofacial Pain
- 17) American College of Nurse Practitioners
- 18) American College of Osteopathic Family Physicians
- 19) American College of Physicians
- 20) American College of Rheumatology
- 21) American Dental Association
- 22) American Dental Education Association
- 23) American Medical Association
- 24) American Medical Directors Association
- 25) American Nurses Association
- 26) American Nurses Credentialing Center
- 27) American Osteopathic Association
- 28) American Osteopathic Association of Addiction Medicine
- 29) American Pain Society
- 30) American Society of Addiction Medicine
- 31) American Society for Pain Management Nursing
- 32) American Society of Anesthesiologists
- 33) American Society of Pain Educators
- 34) Association of American Medical Colleges
- 35) Council of Medical Specialty Societies
- 36) Hospice and Palliative Nurses Association
- 37) National Association of Managed Care Physicians
- 38) National Association of State Controlled Substances Authorities
- 39) National Commission on Certification of Physician Assistants
- 40) National Hospice and Palliative Care Organization
- 41) American College of Emergency Physicians

42) Society of Emergency Medicine Physician Assistants

- h. NDA/ANDA holders will ensure that an interim single toll-free number call center is implemented no later than July 23, 2012, and a fully operational centralized call center is implemented no later than 90 calendar days after the approval of the REMS.

The following materials are part of the ER/LA Opioid Analgesic REMS and are appended:

- [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 1](#)
- [Prescriber Letter 2](#)
- [Prescriber Letter 3](#)
- [Professional Organization/Licensing Board Letter 1](#)
- [Professional Organization/Licensing Board Letter 2](#)
- [ER/LA Opioid Analgesic REMS website \(www.ER-LA-opioidREMS.com\)](#)

II. Implementation System

The ER/LA Opioid Analgesic REMS can be approved without the Elements to Assure Safe Use specifically described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act; therefore an implementation system is not required.

III. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holders will submit each assessment so that it will be received by the FDA on or before the due date based on the initial approval date of the REMS.

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

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME) ^{1,2} or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria](#). Accessed on March 30, 2012.

²Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support](#). Accessed on March 30, 2012.

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

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³ Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. <http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on March 30, 2012.

⁴ Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. <http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on March 30, 2012.

⁵ Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on March 30, 2012.

- ii. Abuse by patient or household contacts.
 - iii. Misuse and addiction.
 - iv. Physical dependence and tolerance.
 - v. Interactions with other medications and substances (See [table in Section VI](#) for specific information).
 - vi. Inadvertent exposure by household contacts, especially children.
- b. Prescribers should assess each patient’s risk of abuse, including substance use and psychiatric history. Prescribers should:
- i. Obtain a complete history and conduct a complete physical examination, including assessment of family history of substance abuse and psychiatric disorders, as well as special considerations for the elderly and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid tolerant patients. (See [table in Section VI](#) for specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability.
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically

evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.

- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
- c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
- d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
- e. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
- f. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
- g. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- g. Prescribers should caution patients that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.

- h. Prescribers should instruct patients to tell all of their doctors about all medications they are taking.
- i. Prescribers should warn patients not to abruptly discontinue or reduce their ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients should call their prescriber for information about managing side effects.
- m. Prescribers should explain that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients to store their ER/LA opioid analgesic in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients to dispose of any ER/LA opioid analgesics when no longer needed and to read the product-specific disposal information included with the ER/LA opioid analgesic product.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic

- hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See [table in Section VI](#) for specific information).
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.
- i. Patients must be opioid tolerant before using any strength of
 - Transdermal fentanyl, or
 - ER hydromorphone.
 - ii. For other ER products, patients must be opioid tolerant before using
 - Certain strengths, or
 - Certain daily doses.
 - iii. See table in Section VI for specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
<p>Avinza (morphine sulfate ER capsules) Dolophine (methadone HCl tablets) Embeda (morphine sulfate ER-naltrexone capsules) Kadian (morphine sulfate ER capsules) Nucynta ER (tapentadol HCl ER tablets) OxyContin (oxycodone HCl CR tablets)</p>	<p>Butrans (buprenorphine transdermal system) Duragesic (fentanyl transdermal system) Exalgo (hydromorphone HCl ER tablets) MS Contin (morphine sulfate CR tablets) Opana ER (oxymorphone HCl ER tablets) Zohydro ER (hydrocodone bitartrate ER capsules)</p>
Dosing Interval	<ul style="list-style-type: none"> ▪ Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> ▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. ▪ Limitations of usage: <ul style="list-style-type: none"> • Not for use as an as-needed analgesic. • Not for mild pain or pain not expected to persist for an extended duration. • Not for use in treating acute pain. ▪ Solid oral dosage forms: <ul style="list-style-type: none"> • Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. • Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. • Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. • Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: <ul style="list-style-type: none"> • Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. • Location of application must be rotated. • Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ See individual product information for the following: <ul style="list-style-type: none"> • Dosage reduction for hepatic or renal impairment.
Drug Interactions Common to the Class	<ul style="list-style-type: none"> ▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ See individual product information for which products: <ul style="list-style-type: none"> • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) <p>See individual product information for additional contraindications.</p>
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application <ul style="list-style-type: none"> • Apply only to sites indicated in the Full Prescribing Information. • Apply to intact/non-irritated skin. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application a minimum of 3 weeks before reapplying to the same site. • Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 8 to 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr
Dosing Interval	Every 72 hours (3 days)
Key Instructions	<ul style="list-style-type: none"> ▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application <ul style="list-style-type: none"> • Apply to intact/non-irritated/non-irradiated skin on a flat surface. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application. • Titrate using no less than 72 hour intervals. • Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. <p>Specific contraindications:</p> <ul style="list-style-type: none"> ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in Opioid-Tolerant	All doses of Duragesic are indicated for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Patients	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg or 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate using a minimum of 3 to 4 day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-patients only
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Use 50 mg every 12 hours as initial dose in opioid nontolerant patients Titrate by 50 mg increments using a minimum of 3-day intervals. Maximum total daily dose is 500 mg Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. Dose once daily in moderate hepatic impairment with 100 mg per day maximum Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Risk of serotonin syndrome Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	<ul style="list-style-type: none"> Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Titrate using a minimum of 2-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	<ul style="list-style-type: none"> ▪ Oxycodone Hydrochloride ▪ Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Zohydro ER	<ul style="list-style-type: none"> ▪ Hydrocodone Bitartrate ▪ Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.
<p>For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.</p>	

Prescriber Letter #1

FDA-Required REMS Program for Serious Drug Risks

Subject: Announcement of a Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose.

Dear **DEA**-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ER/LA opioid analgesics to ensure that the benefits continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS have joined together to implement this REMS for all ER/LA opioid analgesic drug products.

The principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release and Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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

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

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** - Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for your discipline. This training is being developed and will be offered early next year at no or nominal cost to prescribers. You will be notified when REMS-compliant training will become available. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Your Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. The enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) should be used to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as the information in the Medication Guide may have changed.

Prescriber Letter #1

- **Consider Using Other Tools** - In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

A critical component of the ER/LA Opioid Analgesics REMS program is essential safety education for prescribers. REMS-compliant training for prescribers, as described previously, will be delivered by accredited CE providers and will include both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose.

It will be some time before the REMS-compliant training funded by educational grants from the pharmaceutical companies subject to this REMS becomes available. The FDA developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#), which will be used by accredited CE providers to develop REMS-compliant training courses. A follow-up letter notifying you of the availability of REMS-compliant training funded under this REMS will be sent not later than thirty (30) days before such training is offered. However, REMS-compliant education may also be offered by academic institutions or professional societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training offered to improve your ability to prescribe these medications more safely.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

Prescriber Letter #2

FDA-Required REMS Program for Serious Drug Risks

Subject: Availability of Risk Evaluation and Mitigation Strategy (REMS)-compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.

Dear DEA-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid analgesics¹ are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS-compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics – provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

The core messages include:

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to

¹ **The branded and generic drug products subject to this REMS include all:** a) extended-release, oral-dosage forms containing: hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; and c) methadone tablets and solutions that are indicated for use as analgesics.

Prescriber Letter #2

successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** - Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline.
- **Counsel Your Patients** – Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

Prescriber Letter #3

FDA-Required REMS Program for Serious Drug Risks

Subject: Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

Dear DEA-Registered Prescriber:

You are receiving this letter because you recently registered with DEA to prescribe Schedule II or III drugs. The purpose of this letter is to inform you about a Risk Evaluation and Mitigation Strategy (REMS) that has been required by the U.S. Food and Drug Administration (FDA) for all extended-release and long-acting (ER/LA) opioid analgesic drug products.

ER/LA opioid analgesics are used for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

FDA determined that a REMS was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the pharmaceutical companies subject to this REMS have joined together to implement the REMS for all ER/LA opioid analgesic drug products.

The ER/LA Opioid Analgesic REMS has three principal components:

- a) prescriber training on all ER/LA opioid analgesics,
- b) a *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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 that are indicated for use as analgesics.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** - Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Your Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

Prescriber Letter #3

- **Consider Using Other Tools** - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program. REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”), which is being used by accredited CE providers to develop the REMS-compliant training courses. The Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

REMS-compliant training for prescribers includes both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

For a listing of available REMS-compliant training offered by accredited CE providers under the REMS, visit www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics and designed to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to 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. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members– 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

FDA-Required REMS Program for Serious Drug Risks

Subject: Announcement of a Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

Dear <Professional Organization/Licensing Board>:

We encourage you to share the following information with your <members/licensees>.

Extended-release and long-acting (ER/LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ER/LA opioid analgesics to ensure that the benefits continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS have joined together to implement this REMS for all ER/LA opioid analgesic drug products.

The principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release and Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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

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

Prescriber Action

Under the REMS, prescribers are **strongly encouraged** to do **all** of the following:

- **Train (Educate Themselves)** - Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for their discipline. This training is being developed and will be offered early next year at no or nominal cost to prescribers. You will be notified when REMS-compliant training will become available. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Their Patients** - Discuss the safe use, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time they prescribe these medicines. The enclosed *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics* should be used to facilitate these discussions.

Professional Organization/Licensing Board Letter #1

- **Emphasize Understanding the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information in the Medication Guide may have changed.
- **Consider Using other Tools** - In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

A critical component of the ER/LA Opioid Analgesics REMS program is essential safety education for prescribers. REMS-compliant training for prescribers, as described previously, will include both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose.

It will be some time before the REMS-compliant training funded by educational grants from the pharmaceutical companies subject to this REMS becomes available. The FDA developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#), which will be used by accredited CE providers to develop REMS-compliant training courses. A follow-up letter notifying you of the availability of REMS-compliant training funded under this REMS will be sent not later than thirty (30) days before such training is offered. However, REMS-compliant education may also be offered by academic institutions or professional societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training offered to improve your ability to prescribe these medications more safely.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

Prescribers can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

FDA-Required REMS Program for Serious Drug Risks

Subject: Availability of Risk Evaluation and Mitigation (REMS)-compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.

Dear <Professional Organization/Licensing Board>:

Extended-release and long-acting (ER/LA) opioid analgesics¹ are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS-compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics – provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

The core messages include:

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

¹ **The branded and generic drug products subject to this REMS include all:** a) extended-release, oral-dosage forms containing: hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; and c) methadone tablets and solutions that are indicated for use as analgesics.

Professional Organization/Licensing Board Letter #2

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Requested Action

We ask you to encourage your <members/licensees> to successfully complete REMS-compliant training to improve their ability to prescribe these medications more safely. Under the REMS, prescribers are **strongly encouraged** to do **all** of the following:

- **Train (Educate Themselves)** - Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for their discipline.
- **Counsel Their Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions. Prescribers can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)
[Important Safety Information](#)
[Medication Guides](#)
[U.S. Prescribing Information](#)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

The FDA has required a REMS for extended-release and long-acting (ER/LA) opioid analgesics.

Under the conditions specified in this REMS, **prescribers of ER/LA opioid analgesics are strongly encouraged to do all of the following:**

- **Train (Educate Yourself)** - Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) for your discipline
- **Counsel Your Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and/or their caregivers every time you prescribe these medicines. Click here for the [Patient Counseling Document \(PCD\)](#)
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid is dispensed to them
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety, as well as compliance with conditions of treatment, including Patient-Prescriber Agreement (PPA) and risk assessment instruments



[Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program](#)

For additional information about the ER/LA Opioid REMS Program, call 800-503-0784.

Materials for Healthcare Professionals

[ER/LA Opioid Analgesics REMS-Compliant Training](#)

[Dear DEA-Registered Prescriber Letters](#)

[Patient Counseling Document](#)

[Medication Guides](#)

[Healthcare Professional Frequently Asked Questions](#)

Materials for Patients

[Medication Guides](#)

[Patient Frequently Asked Questions](#)

[If you are a Continuing Education provider, click here for more information.](#)



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ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)[Important Safety Information](#)[Medication Guides](#)[U.S. Prescribing Information](#)

ER/LA Opioid Analgesics REMS-Compliant Training

Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of ER/LA opioid analgesics. REMS-compliant training programs will focus on the safe prescribing of ER/LA opioid analgesics.

REMS-compliant training will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

The FDA has developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#), which will be used by Continuing Education (CE) providers to develop the REMS-compliant training programs.

These core messages include:

- Understand how to assess patients for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

The first prescriber REMS-compliant training programs are anticipated to be available by March 1, 2013.

[Click here for a listing of available REMS-compliant training activities supported by educational grants from the ER/LA opioid analgesics companies and offered by accredited CE providers.](#)

Links

[FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#)

[Listing of REMS-compliant training activities from accredited CE providers](#) ^{NEW}

[If you are a CE provider, click here for more information.](#)

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ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

- Home
- Important Safety Information
- Medication Guides
- U.S. Prescribing Information

Patient Counseling Document

What is the Patient Counseling Document?

The Patient Counseling Document (PCD) on Extended-Release/Long Acting (ER/LA) Opioid Analgesics is a tool unique to this REMS designed to facilitate important discussions with your patients for whom you select an ER/LA opioid analgesic. The PCD should be provided to and reviewed with 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.

How can I obtain copies of the PCD?

Printed copies of the PCD can be ordered either through an on-line order or via fax. Detailed instructions for both methods of ordering printed copies of the PCD can be found in the PCD Order Form, and an electronic version of the Patient Counseling Document (PCD) is also available for download.

Materials for Download

[Patient Counseling Document \(PCD\)](#)

[PCD Order Form](#)

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ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)

[Important Safety Information](#)

[Medication Guides](#)

[U.S. Prescribing Information](#)

Dear DEA-Registered Prescriber Letters

Click on the letter title below to open a PDF version of that letter.

- [Dear DEA-Registered Prescriber Letter 1 - Announcing REMS approval](#)
- [Dear DEA-Registered Prescriber Letter 2 - Announcing REMS-related CME/CE opportunities](#)

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

Home

Important Safety Information

Medication Guides

U.S. Prescribing Information

Products covered under the ER/LA Opioid Analgesics REMS Program

Brand Name Products

Trade Name	Generic Name	Company	Contact	Links

Generic Products

Drug Name	Generic Name	Company	Contact	Links

The RPC attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.

Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

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

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

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. **ER/LA opioid analgesics are not indicated for acute pain. Additionally, ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only.** For some of the other ER/LA opioid analgesics, certain dosage strengths or certain doses are for use in opioid-tolerant patients only. Consult the individual Full Prescribing Information for dosing instructions for patients who are not opioid tolerant. 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.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce—refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

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. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. **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 concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm> *or*
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at <http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf>.

Patient Counseling Document and Medication Guide

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 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 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.

Interstitial Pop-Up

The interstitial pop-up is displayed when a website visitor clicks on non-RPC member links on the website pages. The interstitial pop-up is not displayed when a website visitor clicks on the Medication Guides or the U.S. Prescribing Information links on the Products covered under the ER/LA Opioid Analgesics REMS Program page.

Thank you for visiting www.er-la-opioidrems.com.

By clicking "Continue" below, you will be leaving the ER/LA Opioid Analgesics REMS website. RPC is not responsible for the privacy policy, the content or the accuracy of any website accessed through a link.

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
09/23/2013

CLAUDIA B MANZO
09/23/2013
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA/BLA #s: NDA 202880
Products: Zohydro ER (hydrocodone bitartrate) extended-release capsules, 10mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
SPONSOR: Zogenix Inc.
FROM: Judith A. Racoosin, MD, MPH
DATE: September 16, 2013

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 opioids. Because it is important that these products are prescribed

¹<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf>

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 3.8 million unique patients received a dispensed prescription for an ER/LA opioid product from outpatient retail pharmacies.³

B. ER/LA opioid 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 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 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 opioids available as modified-release formulations provides important pain relief options for these patients.

D. The expected duration of treatment with ER/LA opioids 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

E. ER/LA opioid drug products have distinguished themselves among the class of opioid pain medications with their disproportionately high rate of serious adverse

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. *Journal of Pain Research* 2010;3:191-200.

⁶ SDI, Vector One®: National. Years 2000 – 2009, Extracted June 2010.

outcomes including deaths, unintentional overdose, and addiction, in comparison to immediate-release opioid products. The goal of the REMS would be to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioids 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 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. Hydrocodone, the extended release opioid in Zohydro 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 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 products. FDA has determined that ER/LA opioid products 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 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, Zohydro ER will be joining this single shared system REMS.

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

/s/

JUDITH A RACOOSIN
09/21/2013

**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 # 2**

Date: July 25, 2013

Reviewer(s): Danielle Smith, PharmD, MS, Risk Management Analyst
Division of Risk Management

Team Leader: Reema Mehta, PharmD, MPH
Division of Risk Management

Division Director: Claudia Manzo, PharmD
Division of Risk Management

Drug Name(s): Zohydro ER (hydrocodone bitartrate)

Therapeutic Class: Opioid analgesic

Dosage and Route: 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules

Application Type/Number: NDA 202-880

Submission Number: Sequence No. 0022

Applicant/sponsor: Zogenix, Inc.

OSE RCM #: 2012-1666

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

CONTENTS

1	INTRODUCTION	1
1.1	Background	1
1.2	Regulatory History	1
2	MATERIALS REVIEWED	3
2.1	Submissions	3
2.2	Other Materials Informing our review	4
3	SUMMARY OF PROPOSED ER/LA OPIOID ANALGESICS REMS RISK EVALUATION AND MITIGATION STRATEGY	4
4	RECOMMENDATIONS FOR THE REVIEW DIVISION.....	4
5	COMMENTS FOR THE SPONSOR	4
5.1	Element to Assure Safe Use.....	4
5.2	General Comments.....	4
	ATTACHMENTS.....	5

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the Zohydro ER (hydrocodone bitartrate) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 202-880, submitted by Zogenix, Inc. on May 01, 2012 (Sequence No. 0000) and amended on January 11, 2013 (Sequence No. 0016), and May 30, 2013 (Sequence No. 0022).

1.1 BACKGROUND

Zohydro ER (hydrocodone bitartrate), an opioid agonist, is proposed by the Sponsor for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Sponsor's product is a 12-hour extended-release formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS[®]) drug delivery technology. It is available as 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules.

Hydrocodone is currently available as an analgesic only as a combination product with nonnarcotic analgesics such as ibuprofen, acetaminophen, and aspirin. According to the Controlled Substance Act, Schedule III controls apply to hydrocodone combination products containing no more than 300 mg per 100 mL or not more than 15 mg of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. All currently approved combination hydrocodone products fall under Schedule III. However, Zohydro ER, as a single-entity product, would be regulated under Schedule II.

Zohydro ER 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.

1.2 REGULATORY HISTORY

In February 2009, the FDA notified Sponsors of ER/LA opioid analgesics that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. The Sponsors were notified that the REMS would include ER/LA opioid analgesic NDA and ANDA products formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

On May 1, 2012, Zogenix submitted NDA 202-880 for Zohydro ER as a 505(b)2 application, relying on prior findings of safety and efficacy for Vicoprofen[®] (hydrocodone/ibuprofen; NDA 20-716). In the NDA submission, the Sponsor included a REMS proposal, which was an obsolete version of the proposed SSS REMS for ER/LA opioid analgesics.

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 December 7, 2012, the Agency held an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting, in which the committee was asked to determine whether the benefit-risk assessment of Zohydro ER favors its approval for marketing. The committee voted 11-2, with one abstention, against the approval of Zohydro ER. During the AADPAC meeting, the committee was also asked to discuss whether the data supported the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS. The Sponsor provided a summary of additional proposed risk mitigation activities to supplement the ER/LA Opioid Analgesics REMS, which included the following:

1. Commercialize Zohydro ER responsibly
 - a. Focused prescriber target audience – Practitioners who are experienced ER/LA opioid prescribers for chronic pain patients
 - b. Incentivize education and safe use
 - c. Introduce Zohydro ER with a limited top dose strength
2. Augment the ER/LA REMS with their voluntary Zohydro ER Safe-Use initiative that is designed to
 - a. Increase and improve participation in training programs and monitor effectiveness

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. Uphold safe use among patients
 - c. Implement rigorous utilization surveillance systems
 - d. Take corrective actions if issues are detected
3. Share learning and best practices
 - a. Provide practical solutions for home safekeeping for patients
 - b. Improve prescriber training participation and effectiveness
 - c. Expand training across healthcare stakeholders including pharmacists

These voluntary risk mitigation efforts were not submitted to the NDA for Agency review.

The committee felt that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for ER/LA opioids in general, including Zohydro ER. They stated there is a need for additional postmarketing risk mitigation requirements beyond the current REMS for the entire class.

On December 14, 2012, OND informed the Sponsor to submit a revised REMS that is in accordance with the currently approved version (as of August 28, 2012) of the ER/LA REMS and includes all necessary drug-specific information for Zohydro ER. On January 11, 2013, the Sponsor submitted a REMS Amendment to their application, which is the focus of this review.

On February 22, 2013, the Sponsor was sent DRISK interim comments set #1.

On May 30, 2013, the Sponsor amended the proposed REMS (Sequence No. 0022).

On July 23, 2013, the Sponsor was sent a comment to make text visible in the Zohydro ER product-specific information of the FDA Blueprint.

On July 25, 2013, the Agency approved a Prior Approval Supplement (PAS) for the manufacturing of a new 15 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal system. The supplement affected the FDA Blueprint, which was revised to include the new dosage strength. Therefore, a REMS modification to the ER/LA Opioid Analgesics REMS was necessary. The ER/LA Opioid Analgesics REMS modification was also approved at the time of approval on July 25, 2013.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 202-880 for the proposed ER/LA Opioid Analgesics REMS:

- 05/01/2012 Proposed REMS (Sequence No. 0000)
 - 01/11/2013: Amendment 1 (Sequence No. 0016)
 - 05/30/2013: Amendment 2 (Sequence No. 0022)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- ER/LA Opioid Analgesic REMS, approved on July 9, 2012; modified on July 25, 2013
- Division of Risk Management Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set #1 for Zohydro ER (dated February 20, 2013)

3 SUMMARY OF PROPOSED ER/LA OPIOID ANALGESICS REMS RISK EVALUATION AND MITIGATION STRATEGY

The Sponsor proposed no other modifications to the ER/LA Opioid Analgesic REMS other than those proposed by DRISK in interim comments set #1 and email correspondence.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the ER/LA opioid analgesic REMS modification proposal be sent to the Sponsor. Please request that the Sponsor respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS document and materials. Appended to this review is the REMS modification proposal and FDA Blueprint, including our track changes. The Sponsor should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE SPONSOR

5.1 ELEMENT TO ASSURE SAFE USE

5.1.1 FDA Blueprint

On July 25, 2013, Butrans, a member of the ER/LA Opioid Analgesics REMS, had a supplemental NDA approved with a modified "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (Blueprint). Resubmit a proposed modified REMS for your product that adds the 15 mcg/hour intermediate dosage strength of Butrans (buprenorphine) Transdermal System to the FDA Blueprint:

See the attached FDA Blueprint for recommended track changes.

5.2 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS modification for the ER/LA opioid analgesics with attached materials. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document.

ATTACHMENTS

FDA Blueprint

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

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME) ^{1,2} or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria](#). Accessed on March 30, 2012.

²Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support](#). Accessed on March 30, 2012.

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

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³ Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. <http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on March 30, 2012.

⁴ Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. <http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on March 30, 2012

⁵ Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on March 30, 2012.

- ii. Abuse by patient or household contacts.
 - iii. Misuse and addiction.
 - iv. Physical dependence and tolerance.
 - v. Interactions with other medications and substances (See [table in Section VI](#) for specific information).
 - vi. Inadvertent exposure by household contacts, especially children.
- b. Prescribers should assess each patient’s risk of abuse, including substance use and psychiatric history. Prescribers should:
- i. Obtain a complete history and conduct a complete physical examination, including assessment of family history of substance abuse and psychiatric disorders, as well as special considerations for the elderly and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid tolerant patients. (See [table in Section VI](#) for specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability.
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically

evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.

- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
- c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
- d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
- e. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
- f. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
- g. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- g. Prescribers should caution patients that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.

- h. Prescribers should instruct patients to tell all of their doctors about all medications they are taking.
- i. Prescribers should warn patients not to abruptly discontinue or reduce their ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients should call their prescriber for information about managing side effects.
- m. Prescribers should explain that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients to store their ER/LA opioid analgesic in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients to dispose of any ER/LA opioid analgesics when no longer needed and to read the product-specific disposal information included with the ER/LA opioid analgesic product.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic

- hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See [table in Section VI](#) for specific information).
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.
- i. Patients must be opioid tolerant before using any strength of
 - Transdermal fentanyl, or
 - ER hydromorphone.
 - ii. For other ER products, patients must be opioid tolerant before using
 - Certain strengths, or
 - Certain daily doses.
 - iii. See table in Section VI for specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
<p>Avinza (morphine sulfate ER capsules) Dolophine (methadone HCl tablets) Embeda (morphine sulfate ER-naltrexone capsules) Kadian (morphine sulfate ER capsules) Nucynta ER (tapentadol HCl ER tablets) OxyContin (oxycodone HCl CR tablets)</p>	<p>Butrans (buprenorphine transdermal system) Duragesic (fentanyl transdermal system) Exalgo (hydromorphone HCl ER tablets) MS Contin (morphine sulfate CR tablets) Opana ER (oxymorphone HCl ER tablets) Zohydro ER (hydrocodone bitartrate ER capsules)</p>
Dosing Interval	<ul style="list-style-type: none"> ▪ Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> ▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. ▪ Limitations of usage: <ul style="list-style-type: none"> • Not for use as an as-needed analgesic. • Not for mild pain or pain not expected to persist for an extended duration. • Not for use in treating acute pain. ▪ Solid oral dosage forms: <ul style="list-style-type: none"> • Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. • Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. • Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. • Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: <ul style="list-style-type: none"> • Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. • Location of application must be rotated. • Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ See individual product information for the following: <ul style="list-style-type: none"> • Dosage reduction for hepatic or renal impairment.
Drug Interactions Common to the Class	<ul style="list-style-type: none"> ▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ See individual product information for which products: <ul style="list-style-type: none"> • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) <p>See individual product information for additional contraindications.</p>
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 15 mcg/hr , 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application <ul style="list-style-type: none"> • Apply only to sites indicated in the Full Prescribing Information. • Apply to intact/non-irritated skin. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application a minimum of 3 weeks before reapplying to the same site. • Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 10 mcg/hr, 15 mcg/hr , and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 8 to 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr
Dosing Interval	Every 72 hours (3 days)
Key Instructions	<ul style="list-style-type: none"> ▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application <ul style="list-style-type: none"> • Apply to intact/non-irritated/non-irradiated skin on a flat surface. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application. • Titrate using no less than 72 hour intervals. • Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. <p>Specific contraindications:</p> <ul style="list-style-type: none"> ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in Opioid-Tolerant	All doses of Duragesic are indicated for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Patients	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Accidental exposure due to secondary exposure to unwashed/unclotted application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg or 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate using a minimum of 3 to 4 day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-patients only
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Use 50 mg every 12 hours as initial dose in opioid nontolerant patients Titrate by 50 mg increments using a minimum of 3-day intervals. Maximum total daily dose is 500 mg Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. Dose once daily in moderate hepatic impairment with 100 mg per day maximum Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Risk of serotonin syndrome Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	<ul style="list-style-type: none"> Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Titrate using a minimum of 2-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	<ul style="list-style-type: none"> ▪ Oxycodone Hydrochloride ▪ Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Zohydro ER	<ul style="list-style-type: none"> ▪ Hydrocodone Bitartrate ▪ Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.
<p>For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.</p>	

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/s/

DANIELLE SMITH
07/25/2013

KIMBERLY LEHRFELD
07/25/2013

**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: February 20, 2013

Reviewer(s): Danielle Smith, PharmD, MS, Risk Management Analyst
Division of Risk Management

Team Leader: Reema Mehta, PharmD, MPH
Division of Risk Management

Division Director: Claudia Manzo, PharmD
Division of Risk Management

Drug Name(s): Zohydro ER (hydrocodone bitartrate)

Therapeutic Class: Opioid analgesic

Dosage and Route: 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules

Application Type/Number: NDA 202-880

Submission Number: Sequence No. 0016

Applicant/sponsor: Zogenix, Inc.

OSE RCM #: 2012-1666

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

CONTENTS

1	INTRODUCTION	1
1.1	Background	1
1.2	Regulatory History	1
2	MATERIALS REVIEWED	3
2.1	Submissions	3
2.2	Other Materials Informing our review	3
3	SUMMARY OF PROPOSED ER/LA OPIOID ANALGESICS REMS RISK EVALUATION AND MITIGATION STRATEGY	3
3.1	Goals	3
3.2	REMS Elements	4
3.3	REMS Assessment Plan	6
4	RECOMMENDATIONS FOR THE REVIEW DIVISION	6
5	COMMENTS FOR THE SPONSOR	6
5.1	REMS Document	6
5.2	Element to Assure Safe Use	6
5.3	REMS Supporting Document	7
5.4	General Comments	7
	ATTACHMENTS	8

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the Zohydro ER (hydrocodone bitartrate) proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 202-880, submitted by Zogenix, Inc. on May 01, 2012 (Sequence No. 0000) and amended on January 11, 2013 (Sequence No. 0016).

1.1 BACKGROUND

Zohydro ER (hydrocodone bitartrate), an opioid agonist, is proposed by the Sponsor for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Sponsor's product is a 12-hour extended-release formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS[®]) drug delivery technology. It is available as 10, 15, 20, 30, 40 and 50 mg oral extended-release capsules.

Hydrocodone is currently available as an analgesic only as a combination product with nonnarcotic analgesics such as ibuprofen, acetaminophen, and aspirin. According to the Controlled Substance Act, Schedule III controls apply to hydrocodone combination products containing no more than 300 mg per 100 mL or not more than 15 mg of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. All currently approved combination hydrocodone products fall under Schedule III. However, Zohydro ER, as a single-entity product, would be regulated under Schedule II.

Zohydro ER 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.

1.2 REGULATORY HISTORY

In February 2009, the FDA notified Sponsors of ER/LA opioid analgesics that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. The Sponsors were notified that the REMS would include ER/LA opioid analgesic NDA and ANDA products formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

On May 1, 2012, Zogenix submitted NDA 202-880 for Zohydro ER as a 505(b)2 application, relying on prior findings of safety and efficacy for Vicoprofen[®] (hydrocodone/ibuprofen; NDA 20-716). In the NDA submission, the Sponsor included a REMS proposal, which was an obsolete version of the proposed SSS REMS for ER/LA opioid analgesics.

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 December 7, 2012, the Agency held an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting, in which the committee was asked to determine whether the benefit-risk assessment of Zohydro ER favors its approval for marketing. The committee voted 11-2, with one abstention, against the approval of Zohydro ER. During the AADPAC meeting, the committee was also asked to discuss whether the data supported the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS. The Sponsor provided a summary of additional proposed risk mitigation activities to supplement the ER/LA Opioid Analgesics REMS, which included the following:

1. Commercialize Zohydro ER responsibly
 - a. Focused prescriber target audience – Practitioners who are experienced ER/LA opioid prescribers for chronic pain patients
 - b. Incentivize education and safe use
 - c. Introduce Zohydro ER with a limited top dose strength
2. Augment the ER/LA REMS with their voluntary Zohydro ER Safe-Use initiative that is designed to
 - a. Increase and improve participation in training programs and monitor effectiveness

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. Uphold safe use among patients
 - c. Implement rigorous utilization surveillance systems
 - d. Take corrective actions if issues are detected
3. Share learning and best practices
- a. Provide practical solutions for home safekeeping for patients
 - b. Improve prescriber training participation and effectiveness
 - c. Expand training across healthcare stakeholders including pharmacists

These voluntary risk mitigation efforts were not submitted to the NDA for Agency review.

The committee felt that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for ER/LA opioids in general, including Zohydro ER. They stated there is a need for additional postmarketing risk mitigation requirements beyond the current REMS for the entire class.

On December 14, 2012, OND informed the Sponsor to submit a revised REMS that is in accordance with the currently approved version (as of August 28, 2012) of the ER/LA REMS and includes all necessary drug-specific information for Zohydro ER. On January 11, 2013, the Sponsor submitted a REMS Amendment to their application, which is the focus of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 202-880 for the proposed ER/LA Opioid Analgesics REMS:

- 05/01/2012 Proposed REMS (Sequence No. 0000)
 - 01/11/2013: Amendment 1 (Sequence No. 0016)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

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

3 SUMMARY OF PROPOSED ER/LA OPIOID ANALGESICS REMS RISK EVALUATION AND MITIGATION STRATEGY

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 Patient Labeling Team will evaluate the Sponsor's proposed Medication Guide and provide a separate review to DAAAP.

3.2.2 Elements to Assure Safe Use

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

FDA Blueprint

In Section VI. Specific Drug Information for ER/LA Opioid Analgesic Products of the FDA Blueprint, the Sponsor proposed the following information about Zohydro ER:

Zohydro ER	<ul style="list-style-type: none">Hydrocodone BitartrateExtended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none">Every 12 hours
Key Instructions	<ul style="list-style-type: none">Initial dose in opioid non-tolerant patient is 10 mg.Titrate using a minimum of 3-day intervals.Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	<ul style="list-style-type: none">Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone.CYP3A4 inhibitors may increase hydrocodone exposure.CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant	<ul style="list-style-type: none">Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety	None
Relative Potency To Oral	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.

Reviewer Comment:

The Sponsor submitted the original FDA Blueprint approved on July 9, 2012 instead of the revised FDA Blueprint approved on August 24, 2012. DRISK will provide the Sponsor with the most current version of the FDA Blueprint and provide comments on the proposed product-specific information for Zohydro ER.

Prescriber Letters 1, 2, and 3

The Sponsor proposed the following revision for Prescriber Letter 3:

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 that are indicated for use as analgesics.

Reviewer's Comments:

The Sponsor's proposed revision is acceptable. The Sponsor did not propose revisions to Prescriber Letters 1 and 2 because the mailings for these letters have already occurred and will not be sent again.

Organization Letters 1 and 2

There are no recommendations for revisions to the Organization Letters.

Reviewer's Comments:

The Sponsor did not propose revisions to Organization Letters 1 and 2 because the mailings for these letters have already occurred and will not be sent again.

Patient Counseling Document

There are no recommendations for revisions to the Patient Counseling Document.

REMS Website

The Sponsor proposed one modification to the REMS website. The Sponsor added a single row to the table on the 'Products Covered under the ER/LA Opioid Analgesics REMS Program' webpage to include the appropriate information (i.e. brand name, generic name, company name, contact phone number, and links to the U.S. Prescribing Information and Medication Guide).

Reviewer's Comments:

The Sponsor's proposed revision is acceptable. The members of the RPC have submitted a proposed REMS modification, which is currently in review and has a considerable amount of modifications to the REMS website. If Zohydro ER is approved before the proposed REMS modification for the ER/LA Opioid Analgesics REMS is approved, the Sponsor will need to submit a REMS modification incorporating all revisions.

3.2.3 Timetable for Submission of Assessments

There are no recommendations for revisions to the timetable for submission of assessments.

3.3 REMS ASSESSMENT PLAN

There are no recommendations for revisions to the REMS assessment plan.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the ER/LA opioid analgesic REMS modification proposal be sent to the Sponsor. Please request that the Sponsor respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS document and materials. Appended to this review is the REMS modification proposal and FDA Blueprint, including our track changes. The Sponsor should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE SPONSOR

5.1 REMS DOCUMENT

Revise the header of the document to read as:

Initial REMS Approval: 07/2012

Most Recent Modification: XX/2013

5.2 ELEMENT TO ASSURE SAFE USE

5.2.1 FDA Blueprint

A. On August 24, 2012, the Agency approved the following modifications to the FDA Blueprint:

1. Section entitled "Dolophine: Specific Drug Interactions" (page 10) incorrectly stated that:
 - CYP 450 inducers may increase methadone levels
 - CYP 450 inhibitors may decrease methadone levels

The statements were revised to state the following:

- CYP 450 inducers may decrease methadone levels
 - CYP 450 inhibitors may increase methadone levels
2. Addition of the intermediate dosage strengths 40 mg, 70 mg, 130 mg, and 150 mg of Kadian (morphine sulfate extended release) capsules that FDA approved on July 9, 2012 to Section entitled "Kadian" (page 11).

3. Sections entitled “Exalgo: Key Instructions” and “Exalgo: Drug Specific Adverse Reactions” (page 11), which, as approved on July 9, 2012, incorrectly stated:

- Do not use in patients with sulfa allergy—contains sodium metabisulfite.
- Allergic manifestations to sulfa component

The statements were revised to state the following:

- Do not use in patients with sulfite allergy—contains sodium metabisulfite.
 - Allergic manifestations to sulfite component
4. Addition of the newly approved 32 mg dosage strength for Exalgo (Hydromorphone Hydrochloride Extended-Release) tablets that was approved on August 24, 2012 to the section entitled “Exalgo” (page 11).

B. Additionally, the following modification should be made to the subsection entitled *Use in Opioid-Tolerant Patients* under the drug product Kadian:

Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-~~patients~~ only

This statement is revised to allow for greater consistency with the approved labeling.

C. See the attached FDA Blueprint for recommended track changes.

5.2.2 Prescriber Letters

Correct formatting errors in **all** letters (e.g. a question mark (?) appears in all places where a dash (-) should be placed).

5.2.3 Professional Organization Letters

Correct formatting errors in **all** letters (e.g. a question mark (?) appears in all places where a dash (-) should be placed).

5.2.4 ER/LA Opioid Analgesics REMS Website

Hydrocodone should be added to the bulleted list on the Important Safety Information page of REMS website and in the first line of fourth paragraph (pg. 9 of 11)

5.3 REMS SUPPORTING DOCUMENT

The Company name should be added to page 1 of REMS Supporting Document.

5.4 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS modification for the ER/LA opioid analgesics with attached materials. Provide a MS

Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document.

ATTACHMENTS

REMS Document

Patient Counseling Document

FDA Blueprint

Prescriber Letters 1, 2 & 3

Organization Letters 1 & 2

ER/LA Opioid Analgesics REMS Website

Initial REMS Approval: 07/2012

Most Recent Modification: XX/2013

**EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID
ANALGESICS RISK EVALUATION AND MITIGATION
STRATEGY (REMS)**

GOAL

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

I. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid analgesic prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioids are part of the ER/LA Opioid Analgesic REMS program and will be available through the ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com).

B. Elements to Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.
 - a. Training will be considered “REMS-compliant training” under this REMS if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics](#) (“FDA Blueprint”), 3) it includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
 - b. The NDA/ANDA holders of ER/LA opioid analgesic products (“NDA/ANDA holders”) will ensure that REMS-compliant training is made available to prescribers of ER/LA opioid analgesics and will achieve the following performance goals:
 - i. Not later than March 1, 2013, the first REMS-compliant training will be made available.
 - ii. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained;
 - iii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained;
 - iv. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60%

of the 320,000 active prescribers in 2011) will have been trained.

- c. The content of the REMS-compliant training will be based on the learning objectives established by the [FDA Blueprint](#). The FDA Blueprint contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics. The NDA/ANDA holders will direct providers of REMS-compliant training to the FDA Blueprint, via the REMS website (www.ER-LA-opioidREMS.com), and via its Request for Grant Applications. No less than annually, NDA/ANDA holders will direct providers of REMS-compliant training to consult the FDA Blueprint for possible revisions (e.g., changes to the drug specific information).
- d. NDA/ANDA holders will ensure that independent audits of the educational materials used by the providers of REMS-compliant training are conducted. The audits must:
 - i. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
 - ii. Evaluate:
 - 1. whether the content of the training covers all components of the [FDA Blueprint](#) approved as part of the REMS;
 - 2. whether the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - 3. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education[®] (ACCME[®]), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession.
 - iii. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals in [section B.1.b](#).
- e. To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders will make available, and then

maintain, a web site that will contain information about the REMS specified below (www.ER-LA-opioidREMS.com),

- i. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
 - ii. A copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics.
 - iii. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter) (see section B.1.f).
- f. To make prescribers aware of the existence of the REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs:
 - i. [Prescriber Letter 1](#) will be sent not later than 60 days after the initial approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\)](#).
 - ii. [Prescriber Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
 - iii. The prescribers will be identified via the DEA Registration Database.
 - iv. At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and [Prescriber Letter 3](#) will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the [Patient Counseling Document \(PCD\)](#), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.
- g. To further ensure that prescribers are aware of the existence of the ER/LA Opioid Analgesic REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail the following two letters to the professional organizations and state licensing entities

listed in section B.1.g.iii with a request that the information be disseminated to their members:

- i. [Professional Organization/Licensing Board Letter 1](#) will be sent not later than 60 days after the approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\) on Extended-Release/Long-Acting Opioids](#).
- ii. [Professional Organization/Licensing Board Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
- iii. The letter and enclosures referenced above, will be sent to the following entities:
 - a) State Licensing Boards of:
 - 1) Medicine (allopathic and osteopathic)
 - 2) Nursing
 - 3) Dentistry
 - b) Associations of State Licensing Boards:
 - 1) Federation of State Medical Boards
 - 2) National Council of State Boards of Nursing
 - 3) American Association of Dental Boards
 - c) Learned Societies and Professional Associations, including, but not limited to:
 - 1) American Academy of Addiction Psychiatry
 - 2) American Academy of Family Physicians
 - 3) American Academy of Hospice and Palliative Medicine
 - 4) American Academy of Neurology
 - 5) American Academy of Nurse Practitioners
 - 6) American Academy of Nursing
 - 7) American Academy of Orofacial Pain
 - 8) American Academy of Pain Management
 - 9) American Academy of Pain Medicine
 - 10) American Academy of Physical Medicine and Rehabilitation

- 11) American Academy of Physician Assistants
- 12) American Association of Colleges of Osteopathic Medicine
- 13) American Association of Colleges of Nursing
- 14) American Association of Poison Control Centers
- 15) American Board of Medical Specialties
- 16) American Board of Orofacial Pain
- 17) American College of Nurse Practitioners
- 18) American College of Osteopathic Family Physicians
- 19) American College of Physicians
- 20) American College of Rheumatology
- 21) American Dental Association
- 22) American Dental Education Association
- 23) American Medical Association
- 24) American Medical Directors Association
- 25) American Nurses Association
- 26) American Nurses Credentialing Center
- 27) American Osteopathic Association
- 28) American Osteopathic Association of Addiction Medicine
- 29) American Pain Society
- 30) American Society of Addiction Medicine
- 31) American Society for Pain Management Nursing
- 32) American Society of Anesthesiologists
- 33) American Society of Pain Educators
- 34) Association of American Medical Colleges
- 35) Council of Medical Specialty Societies
- 36) Hospice and Palliative Nurses Association
- 37) National Association of Managed Care Physicians
- 38) National Association of State Controlled Substances Authorities
- 39) National Commission on Certification of Physician Assistants
- 40) National Hospice and Palliative Care Organization

- 41) American College of Emergency Physicians
- 42) Society of Emergency Medicine Physician Assistants

- h. NDA/ANDA holders will ensure that an interim single toll-free number call center is implemented no later than July 23, 2012, and a fully operational centralized call center is implemented no later than 90 calendar days after the approval of the REMS.

The following materials are part of the ER/LA Opioid Analgesic REMS and are appended:

- 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 1
- Prescriber Letter 2
- Prescriber Letter 3
- Professional Organization/Licensing Board Letter 1
- Professional Organization/Licensing Board Letter 2
- ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com)

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II. Implementation System

The ER/LA Opioid Analgesic REMS can be approved without the Elements to Assure Safe Use specifically described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act; therefore an implementation system is not required.

III. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA/ANDA holders will submit each assessment so that it will be received by the FDA on or before the due date based on the initial approval date of the REMS.

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

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME)^{1,2} or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria](#). Accessed on March 30, 2012.

²Accreditation Council for Continuing Medical Education. 2012. [Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support](#). Accessed on March 30, 2012.

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

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³ Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table, Table 7.1.a.* Rockville, MD. <http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on March 30, 2012.

⁴ Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits, Table 19.* Rockville, MD. <http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on March 30, 2012

⁵ Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81.* December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on March 30, 2012.

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- ii. Abuse by patient or household contacts.
 - iii. Misuse and addiction.
 - iv. Physical dependence and tolerance.
 - v. Interactions with other medications and substances (See table in Section VI for specific information).
 - vi. Inadvertent exposure by household contacts, especially children.
- b. Prescribers should assess each patient's risk of abuse, including substance use and psychiatric history. Prescribers should:
- i. Obtain a complete history and conduct a complete physical examination, including assessment of family history of substance abuse and psychiatric disorders, as well as special considerations for the elderly and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid tolerant patients. (See [table in Section VI for specific information](#)).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability.
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically

- evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
 - c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
 - d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
 - e. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
 - f. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
 - g. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
- g. Prescribers should caution patients that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.

- h. Prescribers should instruct patients to tell all of their doctors about all medications they are taking.
- i. Prescribers should warn patients not to abruptly discontinue or reduce their ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients should call their prescriber for information about managing side effects.
- m. Prescribers should explain that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients to store their ER/LA opioid analgesic in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients to dispose of any ER/LA opioid analgesics when no longer needed and to read the product-specific disposal information included with the ER/LA opioid analgesic product.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic

- hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See [table in Section VI for specific information](#)).
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.
- i. Patients must be opioid tolerant before using any strength of
 - Transdermal fentanyl, or
 - ER hydromorphone.
 - ii. For other ER products, patients must be opioid tolerant before using
 - Certain strengths, or
 - Certain daily doses.
 - iii. See table in Section VI for specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

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VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)													
<table border="0"> <tr> <td>Avinza (morphine sulfate ER capsules)</td> <td>Butrans (buprenorphine transdermal system)</td> </tr> <tr> <td>Dolophine (methadone HCl tablets)</td> <td>Duragesic (fentanyl transdermal system)</td> </tr> <tr> <td>Embeda (morphine sulfate ER-naltrexone capsules)</td> <td>Exalgo (hydromorphone HCl ER tablets)</td> </tr> <tr> <td>Kadian (morphine sulfate ER capsules)</td> <td>MS Contin (morphine sulfate CR tablets)</td> </tr> <tr> <td>Nucynta ER (tapentadol HCl ER tablets)</td> <td>Opana ER (oxymorphone HCl ER tablets)</td> </tr> <tr> <td>OxyContin (oxycodone HCl CR tablets)</td> <td>Zohydro ER (hydrocodone bitartrate ER capsules)</td> </tr> </table>		Avinza (morphine sulfate ER capsules)	Butrans (buprenorphine transdermal system)	Dolophine (methadone HCl tablets)	Duragesic (fentanyl transdermal system)	Embeda (morphine sulfate ER-naltrexone capsules)	Exalgo (hydromorphone HCl ER tablets)	Kadian (morphine sulfate ER capsules)	MS Contin (morphine sulfate CR tablets)	Nucynta ER (tapentadol HCl ER tablets)	Opana ER (oxymorphone HCl ER tablets)	OxyContin (oxycodone HCl CR tablets)	Zohydro ER (hydrocodone bitartrate ER capsules)
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Nucynta ER (tapentadol HCl ER tablets)	Opana ER (oxymorphone HCl ER tablets)												
OxyContin (oxycodone HCl CR tablets)	Zohydro ER (hydrocodone bitartrate ER capsules)												
Dosing Interval	<ul style="list-style-type: none"> Refer to individual product information. 												
Key Instructions	<ul style="list-style-type: none"> Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. If pain increases, attempt to identify the source, while adjusting the dose. When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. Limitations of usage: <ul style="list-style-type: none"> Not for use as an as-needed analgesic. Not for mild pain or pain not expected to persist for an extended duration. Not for use in treating acute pain. Solid oral dosage forms: <ul style="list-style-type: none"> Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. Dispose of unused product by flushing down the toilet. Transdermal dosage forms: <ul style="list-style-type: none"> Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. Location of application must be rotated. Prepare skin by clipping, not shaving hair, and washing area only with water. See individual product information for the following: <ul style="list-style-type: none"> Dosage reduction for hepatic or renal impairment. 												
Drug Interactions Common to the Class	<ul style="list-style-type: none"> Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use. 												

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Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ See individual product information for which products: <ul style="list-style-type: none"> • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) <p>See individual product information for additional contraindications.</p>
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application <ul style="list-style-type: none"> • Apply only to sites indicated in the Full Prescribing Information. • Apply to intact/non-irritated skin. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application a minimum of 3 weeks before reapplying to the same site. • Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg

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Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 8 to 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr
Dosing Interval	Every 72 hours (3 days)
Key Instructions	<ul style="list-style-type: none"> ▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application <ul style="list-style-type: none"> • Apply to intact/non-irritated/non-irradiated skin on a flat surface. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application. • Titrate using no less than 72 hour intervals. • Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. <p>Specific contraindications:</p> <ul style="list-style-type: none"> ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in Opioid-Tolerant	All doses of Duragesic are indicated for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Patients	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Accidental exposure due to secondary exposure to unwashed/unclothed application site. Increased drug exposure with increased core body temperature or fever. Bradycardia Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Initial dose as first opioid: 20 mg/0.8 mg. Titrate using a minimum of 3-day intervals. Swallow capsules whole (do not chew, crush, or dissolve) Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg , or 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> Use the conversion ratios in the individual product information. Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. Titrate using a minimum of 3 to 4 day intervals. Swallow tablets whole (do not chew, crush, or dissolve). Do not use in patients with <u>sulfa-sulfite</u> allergy—contains sodium
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to <u>sulfa-sulfite</u> component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, <u>40 mg</u> , 50 mg, 60 mg, <u>70 mg</u> , <u>80 mg</u> , <u>100 mg</u> , <u>130 mg</u> , <u>150 mg</u> , and <u>200 mg</u>
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 2-day intervals. Swallow capsules whole (do not chew, crush, or dissolve).

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, <u>130 mg, 150 mg</u> , and 200 mg capsules are for use in opioid-tolerant patients <u>only</u> .
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> Product information recommends not using as first opioid. Titrate using a minimum of 2-day intervals. Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Use 50 mg every 12 hours as initial dose in opioid nontolerant patients Titrate by 50 mg increments using a minimum of 3-day intervals. Maximum total daily dose is 500 mg Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. Dose once daily in moderate hepatic impairment with 100 mg per day maximum Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Risk of serotonin syndrome Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	<ul style="list-style-type: none"> Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	<ul style="list-style-type: none"> Titrate using a minimum of 2-day intervals. Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	<ul style="list-style-type: none"> Oxycodone Hydrochloride Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. Titrate using a minimum of 1 to 2 day intervals. Hepatic impairment: start with one third to one half the usual dosage Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	<ul style="list-style-type: none"> CYP3A4 inhibitors may increase oxycodone exposure. CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Zohydro ER	<ul style="list-style-type: none"> Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patient is 10 mg. Titrate using a minimum of 3-day intervals. Swallow capsules whole (do not chew, crush, or dissolve <u>or open the capsule</u>).
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. CYP3A4 inhibitors may increase hydrocodone exposure. CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.

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For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

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Subject: Announcement of a Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose.

Dear DEA-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ER/LA opioid analgesics to ensure that the benefits continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS have joined together to implement this REMS for all ER/LA opioid analgesic drug products.

The principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release and Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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

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

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for your discipline. This training is being developed and will be offered early next year at no or nominal cost to prescribers. You will be notified when REMS-compliant training will become available. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Your Patients** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. The enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) should be used to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as the information in the Medication Guide may have changed.

Prescriber Letter #1

- **Consider Using Other Tools** In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

A critical component of the ER/LA Opioid Analgesics REMS program is essential safety education for prescribers. REMS-compliant training for prescribers, as described previously, will be delivered by accredited CE providers and will include both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose.

It will be some time before the REMS-compliant training funded by educational grants from the pharmaceutical companies subject to this REMS becomes available. The FDA developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#), which will be used by accredited CE providers to develop REMS-compliant training courses. A follow-up letter notifying you of the availability of REMS-compliant training funded under this REMS will be sent not later than thirty (30) days before such training is offered. However, REMS-compliant education may also be offered by academic institutions or professional societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training offered to improve your ability to prescribe these medications more safely.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

FDA Required REMS Program for Serious Drug Risks

Subject: Availability of Risk Evaluation and Mitigation Strategy (REMS) compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.

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Dear DEA-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid analgesics¹ are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics – provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. *REMS compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

The core messages include:

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to

¹ **The branded and generic drug products subject to this REMS include all:** a) extended-release, oral-dosage forms containing: [hydrocodone](#), hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; *and* c) methadone tablets and solutions that are indicated for use as analgesics.

Prescriber Letter #2

successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** ☑ Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline.
- **Counsel Your Patients** – Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended☑Release/Long☑Acting Opioid Analgesics* (PCD) to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** ☑ Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.
- **Consider Using Other Tools** ☑ In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended☑Release/Long☑Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

FDA Required REMS Program for Serious Drug Risks

Subject: Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

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Dear DEA-Registered Prescriber:

You are receiving this letter because you recently registered with DEA to prescribe Schedule II or III drugs. The purpose of this letter is to inform you about a Risk Evaluation and Mitigation Strategy (REMS) that has been required by the U.S. Food and Drug Administration (FDA) for all extended-release and long-acting (ER/LA) opioid analgesic drug products.

ER/LA opioid analgesics are used for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

FDA determined that a REMS was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the pharmaceutical companies subject to this REMS have joined together to implement the REMS for all ER/LA opioid analgesic drug products.

The ER/LA Opioid Analgesic REMS has three principal components:

- a) prescriber training on all ER/LA opioid analgesics,
- b) a *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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 that are indicated for use as analgesics.

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Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself)** Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Your Patients** – Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

Prescriber Letter #3

- **Consider Using Other Tools** In addition to the PCD, there are other publicly available tools to improve patient, household and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program. REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), which is being used by accredited CE providers to develop the REMS-compliant training courses. The Blueprint is available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>

REMS-compliant training for prescribers includes both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

For a listing of available REMS-compliant training offered by accredited CE providers under the REMS, visit www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics and designed to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to 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. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members– 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.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

FDA Required REMS Program for Serious Drug Risks

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Subject: Announcement of a Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

Dear <Professional Organization/Licensing Board>:

We encourage you to share the following information with your <members/licensees>.

Extended-release and long-acting (ER/LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ER/LA opioid analgesics to ensure that the benefits continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS have joined together to implement this REMS for all ER/LA opioid analgesic drug products.

The principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
- b) the *Patient Counseling Document on Extended-Release and Long-Acting Opioid Analgesics* (PCD), and
- c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

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

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

Prescriber Action

Under the REMS, prescribers are **strongly encouraged** to do **all** of the following:

- **Train (Educate Themselves)** Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for their discipline. This training is being developed and will be offered early next year at no or nominal cost to prescribers. You will be notified when REMS-compliant training will become available. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (“FDA Blueprint”); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.
- **Counsel Their Patients** Discuss the safe use, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time they prescribe these medicines. The enclosed *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics* should be used to facilitate these discussions.

Professional Organization/Licensing Board Letter #1

- **Emphasize Understanding the Medication Guide** ☐ Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information in the Medication Guide may have changed.
- **Consider Using other Tools** ☐ In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

A critical component of the ER/LA Opioid Analgesics REMS program is essential safety education for prescribers. REMS-compliant training for prescribers, as described previously, will include both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose.

It will be some time before the REMS-compliant training funded by educational grants from the pharmaceutical companies subject to this REMS becomes available. The FDA developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \("FDA Blueprint"\)](#) which will be used by accredited CE providers to develop REMS-compliant training courses. A follow-up letter notifying you of the availability of REMS-compliant training funded under this REMS will be sent not later than thirty (30) days before such training is offered. However, REMS-compliant education may also be offered by academic institutions or professional societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training offered to improve your ability to prescribe these medications more safely.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their specific ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. 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 members – 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.

Prescribers can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

DPOLB Letter 1

Page 2 of 2

FDA Required REMS Program for Serious Drug Risks

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Subject: Availability of Risk Evaluation and Mitigation (REMS) compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.

Dear <Professional Organization/Licensing Board>:

Extended-release and long-acting (ER/LA) opioid analgesics¹ are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

- a) Prescriber training on all ER/LA opioid analgesics,
b) the Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD), and
c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics - provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. REMS compliant training will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

The core messages include:

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
• Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
• Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
• Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
• Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

1 The branded and generic drug products subject to this REMS include all: a) extended-release, oral-dosage forms containing hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; and c) methadone tablets and solutions that are indicated for use as analgesics.

Professional Organization/Licensing Board Letter #2

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Requested Action

We ask you to encourage your <members/licensees> to successfully complete REMS-compliant training to improve their ability to prescribe these medications more safely. Under the REMS, prescribers are **strongly encouraged** to do **all** of the following:

- **Train (Educate Themselves)** ☐ Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for their discipline.
- **Counsel Their Patients** – Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions. Prescribers can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** ☐ Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.
- **Consider Using Other Tools** ☐ In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
 - by phone at 1-800-FDA-1088 (1-800-332-1088) or
 - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)

[Important Safety Information](#)

[Medication Guides](#)

[U.S. Prescribing Information](#)

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics.

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.

ER/LA opioid analgesics companies have worked with the FDA to develop materials for the REMS program to educate and inform healthcare professionals on the safe prescribing of ER/LA opioid analgesics. In addition, CE providers are developing independent CE-accredited educational activities that focus on the safe prescribing of ER/LA opioid analgesics.

Under the conditions specified in this REMS, prescribers of ER/LA opioid analgesics are strongly encouraged to do all of the following:

- **Train (Educate Yourself)** - Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) for your discipline
- **Counsel Your Patients** - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and/or their caregivers every time you prescribe these medicines. Click here for the [Patient Counseling Document \(PCD\)](#)
- **Emphasize Patient and Caregiver Understanding of the Medication Guide** - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid is dispensed to them
- **Consider Using Other Tools** - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety, as well as compliance with conditions of treatment, including Patient-Prescriber Agreement (PPA) and risk assessment instruments



[Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program](#)

Materials for Healthcare Professionals

[ER/LA Opioid Analgesics REMS-Compliant Training](#)

[Dear DEA-Registered Prescriber Letters](#)

[Patient Counseling Document](#)

[Medication Guides](#)

[Healthcare Professional Frequently Asked Questions \(Coming Soon\)](#)

Materials for Patients

[Medication Guides](#)

[Patient Frequently Asked Questions \(Coming Soon\)](#)

If you are a Continuing Education provider, [click here for more information.](#) (Coming Soon)

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

Home

Important Safety Information

Medication Guides

U.S. Prescribing Information

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics.

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.

ER/LA opioid analgesics companies have worked with the FDA to develop materials for the REMS program to educate and inform healthcare professionals on the safe prescribing of ER/LA opioid analgesics. In addition, CE providers are developing independent CE-accredited educational activities that focus on the safe prescribing of ER/LA opioid analgesics.

Under the conditions specified in this REMS, prescribers of ER/LA opioid analgesics are strongly encouraged to do all of the following:

- Train (Educate Yourself) - Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) for your discipline
- Counsel Your Patients - Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and/or their caregivers every time you prescribe these medicines. Click here for the [Patient Counseling Document \(PCD\)](#)
- Emphasize Patient and Caregiver Understanding of the Medication Guide - Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid is dispensed to them
- Consider Using Other Tools - In addition to the PCD, there are other publicly available tools to improve patient, household and community safety, as well as compliance with conditions of treatment, including Patient-Prescriber Agreement (PPA) and risk assessment instruments

[Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program](#)

For additional information about the ER/LA Opioid REMS Program, call 800-503-0784

Materials for Healthcare Professionals

[ER/LA Opioid Analgesics REMS-Compliant Training](#)

[Dear DEA-Registered Prescriber Letters](#)

[Patient Counseling Document](#)

[Medication Guides](#)

Healthcare Professional Frequently Asked Questions (Coming Soon)

Materials for Patients

[Medication Guides](#)

Patient Frequently Asked Questions (Coming Soon)

If you are a Continuing Education provider, click here for more information. (Coming Soon)

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

Home

Important Safety Information

Medication Guides

U.S. Prescribing Information

ER/LA Opioid Analgesics REMS-Compliant Training

Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of ER/LA opioid analgesics. REMS-compliant training programs will focus on the safe prescribing of ER/LA opioid analgesics.

REMS-compliant training will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

The FDA has developed core messages to be communicated to prescribers in the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \(FDA Blueprint\)](#), which will be used by Continuing Education (CE) providers to develop the REMS-compliant training programs.

These core messages include:

- Understand how to assess patients for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

The first prescriber REMS-compliant training programs are anticipated to be available by March 1, 2013.

Click here for a listing of available REMS-compliant training programs supported by educational grants from the ER/LA opioid analgesics companies and offered by accredited CE providers (Coming Soon)

Links

[FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \(FDA Blueprint\)*](#)

[Listing of REMS-compliant training programs from accredited CE providers \(Coming Soon\)](#)

[If you are a CE provider, click here for more information. \(Coming Soon\)](#)

ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid
Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)

[Important Safety Information](#)

[Medication Guides](#)

[U.S. Prescribing Information](#)

Dear DEA-Registered Prescriber Letters

Click on the letter title below to open a PDF version of that letter.

- [Dear DEA-Registered Prescriber Letter 1 - Announcing REMS approval](#)
-

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ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

[Home](#)

[Important Safety Information](#)

[Medication Guides](#)

[U.S. Prescribing Information](#)

Patient Counseling Document

What is the Patient Counseling Document?

The Patient Counseling Document (PCD) on Extended-Release/Long Acting (ER/LA) Opioid Analgesics is a tool unique to this REMS designed to facilitate important discussions with your patients for whom you select an ER/LA opioid analgesic. The PCD should be provided to and reviewed with 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.

How can I obtain copies of the PCD?

Printed copies of the PCD can be ordered either through an on-line order or via fax. Detailed instructions for both methods of ordering printed copies of the PCD can be found in the PCD Order Form, and an electronic version of the Patient Counseling Document (PCD) is also available for download.

Materials for Download

[Patient Counseling Document \(PCD\)](#)

[PCD Order Form](#)

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ER/LA Opioid Analgesics REMS

The Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy

Home

Important Safety Information

Medication Guides

U.S. Prescribing Information

Products covered under the ER/LA Opioid Analgesics REMS Program

Brand Name Products

Trade Name	Generic Name	Company	Contact	Links
Avinza®	Morphine sulfate extended-release capsules	Pfizer Inc.	1-800-438-1985	- U.S. Prescribing Information - Medication Guide
Butrans®	Buprenorphine transdermal system	Purdue Pharma L.P.	1-888-726-7535	- U.S. Prescribing Information - Medication Guide
Dolophine®	Methadone hydrochloride tablets	Roxane Laboratories, Inc.	1-800-962-8364	- U.S. Prescribing Information - Medication Guide
Duragesic®	Fentanyl transdermal system	Janssen Pharmaceuticals, Inc.	1-800-526-7736	- U.S. Prescribing Information - Medication Guide
***Embeda®	Morphine sulfate and naltrexone extended-release capsules	Pfizer Inc.	1-800-438-1985	- U.S. Prescribing Information - Medication Guide
EXALGO®	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt	1-800-778-7898	- U.S. Prescribing Information - Medication Guide
Kadian®	Morphine sulfate extended-release capsules	Actavis	1-888-496-3082	- U.S. Prescribing Information - Medication Guide
MS Contin®	Morphine sulfate controlled-release tablets	Purdue Pharma L.P.	1-888-726-7535	- U.S. Prescribing Information - Medication Guide
Nucynta® ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals, Inc.	1-800-526-7736	- U.S. Prescribing Information - Medication Guide
Opana® ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals Inc.	1-800-462-3636	- U.S. Prescribing Information - Medication Guide
OxyContin®	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma L.P.	1-888-726-7535	- U.S. Prescribing Information - Medication Guide
*Palladone®	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma L.P.	1-888-726-7535	- U.S. Prescribing Information - Medication Guide
Zohydro™ ER	<u>Hydrocodone bitartrate extended release capsules</u>	<u>Zogenix Inc.</u>	<u>1-866-964-3649</u>	<u>- U.S. Prescribing Information</u> <u>- Medication Guide</u>

*No longer being marketed, but is still approved.

***Not currently available or marketed due to a voluntary recall, but is still approved.

Page 6 of 11

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Generic Products

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Drug Name	Generic Name	Company	Contact	Links
Fentanyl	Fentanyl extended-release transdermal system	Actavis	1-877-422-7452	. U.S. Prescribing Information . Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Mallinckrodt	1-800-778-7898	. U.S. Prescribing Information . Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies Inc.	1-877-446-3679	. U.S. Prescribing Information . Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Noven Pharmaceuticals Inc.	1-800-667-4708	. U.S. Prescribing Information . Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Sandoz Inc.	1-800-525-8747	. U.S. Prescribing Information . Medication Guide
Fentanyl	Fentanyl transdermal system	Watson Laboratories Inc	1-800-272-5525	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Mallinckrodt	1-800-778-7898	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Roxane Laboratories, Inc.	1-800-962-8364	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride IntenSol™ oral concentrate	Roxane Laboratories Inc.	1-800-962-8364	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride Oral Solution	Roxane Laboratories Inc.	1-800-962-8364	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Sandoz Inc.	1-800-525-8747	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride Tablets	ThePharmaNetwork LLC	1-877-272-7901	. U.S. Prescribing Information . Medication Guide
Methadone Hydrochloride	Methadone hydrochloride oral solution	VistaPharm Inc.	(727) 530-1633	. U.S. Prescribing Information . Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Vintage Pharmaceuticals LLC d/b/a Qualitest Pharmaceuticals	1-800-444-4011	. U.S. Prescribing Information . Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Mallinckrodt	1-800-778-7898	. U.S. Prescribing Information . Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Mylan Pharmaceuticals Inc.	1-877-446-3679	. U.S. Prescribing Information . Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Rhodes Pharmaceuticals L.P.	1-888-827-0616	. U.S. Prescribing Information . Medication Guide
Morphine Sulfate	Morphine sulfate extended-release capsules	Watson Laboratories Inc	1-800-272-5525	. U.S. Prescribing Information . Medication Guide
Oxycodone Hydrochloride	**Oxycodone hydrochloride extended-release tablets	Vintage Pharmaceuticals LLC d/b/a Qualitest Pharmaceuticals	1-800-444-4011	. U.S. Prescribing Information . Medication Guide

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Oxycodone Hydrochloride	**Oxycodone hydrochloride extended-release tablets	Mallinckrodt	1-800-778-7898	. U.S. Prescribing Information . Medication Guide
Oxymorphone Hydrochloride	Oxymorphone hydrochloride extended-release tablets	Actavis	1-800-422-8534	. U.S. Prescribing Information . Medication Guide

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[**Tentatively approved products.](#)

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[Page 6 of 11](#)

[Page 8 of 11](#)

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Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

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

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

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These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, [hydrocodone](#), hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. ER/LA opioid analgesics are not indicated for acute pain. Additionally, ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only. For some of the other ER/LA opioid analgesics, certain dosage strengths or certain doses are for use in opioid-tolerant patients only. Consult the individual Full Prescribing Information for dosing instructions for patients who are not opioid tolerant. 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.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.



APPEARS THIS WAY ON ORIGINAL,

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce—refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

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. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. 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 concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with

Page 10 of 11

transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm> or
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at <http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf>.

Patient Counseling Document and Medication Guide

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 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 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.

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/s/

DANIELLE SMITH
02/20/2013

REEMA J MEHTA
02/20/2013