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

REMS MODIFICATION REVIEW

Date:	August 18, 2014
Reviewers:	Joan E. Blair, R.N., M.P.H. Risk Management/Health Communications Analyst Division of Risk Management (DRISK) Danny Gonzalez, M.S., Pharm.D. Risk Management Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm.D. DRISK
Acting Deputy Division Director	Reema Mehta, Pharm.D, M.P.H. DRISK
Drug Name(s):	See table below
Therapeutic Class:	Opioid Agonist: Extended-Release and Long-Acting Opioid Analgesic Drug Products

Drug Name	Dosage and Route	Application Type/Number	Submission Number (eCTD)	Applicant/ Sponsor	Date Received
Avinza (morphine sulfate)	extended-release capsules	NDA 021260	033 0037	King	6/13/14 8/6/14
Butrans (buprenorphine)	Transdermal System	NDA 021306	0117 0123	Purdue	6/12/14 8/4/14
Dolophine (methadone hydrochloride)	tablets	NDA 006134	0026 144	Roxane	6/11/14 8/6/14
Methadone	oral solution	ANDA 087997	0024 0025	Roxane	7/17/14 8/8/2014
Methadone oral solution	oral solution	ANDA 087393	0027 0028	Roxane	7/16/14 8/7/2014

Methadone	oral concentrate	ANDA 089897	0023 0024	Roxane	7/16/14 8/6/2014
Duragesic (Fentanyl Transdermal System)	Transdermal system	NDA 019813	0111 0116	Ortho-McNeil	6/12/14 8/7/14
Embeda (morphine sulfate and naltrexone hydrochloride)	extended-release capsules	NDA 022321	102 0108	Alpharma/King	6/13/14 8/6/14
Exalgo (hydromorphone HCl)	extended-release capsules	NDA 021217	132 136	Mallinkrodt	6/13/14 8/8/14
Kadian (morphine sulfate)	extended-release capsules	NDA 020616	0041 0042 0044	Actavis	6/9/14 7/2/2014 8/4/2014
MS Contin (morphine sulfate)	controlled-release tablets	NDA 019516	0044 0049	Purdue	6/12/14 8/4/14
Nucynta ER (tapentadol)	extended-release oral tablets	NDA 200533	0118 0124	Ortho-McNeil	6/11/14 8/6/14
Opana ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	106 110	Endo	6/13/14 8/7/14
Opana ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 021610	0060 0063	Endo	6/13/14 8/7/14
Oxycontin (oxycodone hydrochloride)	controlled-release tablets	NDA 022272	203 0208	Purdue	6/12/14 8/4/14
Zohydro ER (hydrocodone bitartate)	extended-release oral capsules	NDA 202880	87 0044	Zogenix	6/13/14 8/8/14
Targiniq (oxycodone hydrochloride and naloxone hydrochloride)	extended-release tablets	NDA 205777	0038 0042	Purdue	7/21/14 8/4/14
morphine sulfate ER cap	extended-release oral capsules	ANDA 079040	0041	Actavis Elizabeth, LLC	7/10/2014 8/4/2014

fentanyl transdermal system	Transdermal System	ANDA 077449	0014 0015	Avenva , An Apotex Company	7/9/2014 8/4/2014
methadone HCL tablet	tablet	ANDA 040050	0033 0034	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
methadone HCL tab	Tablet	ANDA 040517	0034 0035	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 076412	0034 0035	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 076438	0032 0033	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
fentanyl transdermal system	Transdermal System	ANDA 077154	0051 0052	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 200824	0037 0039	Mylan Pharmaceuticals Inc.	7/10/2014 8/6/2014
fentanyl transdermal system	Transdermal System	ANDA 076258	0040 0041	Mylan Technologies Inc.	7/10/2014 8/6/2014
fentanyl transdermal system	Transdermal System	ANDA 077775	0092 0093	Noven Pharmaceuticals, Inc.	7/17/2014 8/13/2014
fentanyl transdermal system	Transdermal System	ANDA 077062	0044 0045	Par Pharmaceuticals, Inc.	7/17/2014 8/5/2014
morphine sulfate ER cap	extended-release oral capsules	ANDA 200812	0035 0036	Par Pharmaceuticals, Inc.	7/17/2014 8/5/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 078761	0020 0021	Ranbaxy Laboratories, Inc.	7/17/2014 8/7/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 074769	0035 0038	Rhodes Pharmaceuticals L.P.	7/11/2014 8/6/2014
morphine sulfate ER tab	extended-release oral tablets	ANDA 074862	0038 0041	Rhodes Pharmaceuticals L.P.	7/11/2014 8/6/2014
methadone HCL tablet	tablet	ANDA 040241	Not applicable	Sandoz Inc.	7/14/2014 8/5/2014

methadone HCL tablet	tablet	ANDA 090635	0026 0027	ThePharmaNetwork, LLC	7/16/2014 8/11/2014
morphine sulfate extended release capsules	extended-release oral capsules	ANDA 202104	Not applicable	Upsher-Smith	7/16/2014 8/8/2014
morphine sulfate extended-release tablets	extended-release oral tablets	ANDA 075295	0031 0035	Vintage Pharmaceuticals LLC, d/b/a Qualitest Pharmaceuticals and a subsidiary of Endo Pharmaceuticals Inc.	7/14/2014 8/8/2014
fentanyl transdermal system	Transdermal System	ANDA 076709	0139 0140	Watson Laboratories, Inc.	7/10/2014 8/6/2014
oxymorphone HCl extended-release	extended-release oral tablets	ANDA 200822	0025 0027	Roxane Labs, Inc.	7/17/2014 8/6/2014
hydromorphone HCl extended-release	extended-release oral tablets	ANDA 202144	0039 0040	Actavis Laboratories FL, Inc.	7/17/2014 8/5/2014
(b) (4)					
oxymorphone HCl extended-release	extended-release oral tablets	ANDA 202946	0020 0021	Mallinckrodt Pharmaceuticals	7/18/2014 8/8/2014
oxymorphone HCl extended-release	extended-release oral tablets	ANDA 079046	0058 0059	Actavis South Atlantic, L.L.C.	7/10/2014 8/4/2014
oxymorphone HCl extended-release	extended-release oral tablets	ANDA 079087	0032 0033	Impax Labs, Inc.	7/16/2014 8/5/2014
methadone HCl	oral solution	ANDA 090707	0021 0022	Vistapharm	7/17/2014 8/5/2014

RCM #: 2012-2535

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

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EXECUTIVE SUMMARY

This memorandum documents the Division of Risk Management's (DRISK) final review of the proposed single-shared system (SSS) Risk Evaluation and Mitigation Strategy (REMS) modification for the extended-release and long-acting opioid analgesics, or 'ER/LA opioids'.[1] NDA/ANDA holders submitted the proposed REMS modification to their respective applications between June 9, 2014 and June 13, 2014. Their final REMS submissions were submitted between August 4, 2014 and August 13, 2014.

On September 10, 2013, FDA announced class-wide safety labeling changes (SLC) and new post-market study requirements for all ER/LA opioid analgesics intended to treat pain. The revised label information noted that ER/LA opioids 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 SLC also proposed revisions to the boxed warning for all ER/LA opioids in order to standardize them among these products, including information about the risk of addiction, abuse, misuse; risk of respiratory depression; risk of accidental ingestion; risk of neonatal opioid withdrawal syndrome (NOWS); and risk of overdose with concomitant CYP3A4 inhibitors and inducers.

The proposed modified REMS consists of product specific Medication Guides, elements to assure safe use, and a timetable for submission of assessments of the REMS. The proposed modifications to the REMS consist of revisions to the ER/LA REMS Document, appended materials[2], and REMS Supporting Document (SD).

DRISK finds the proposed modifications to the ER/LA Opioid Analgesics REMS to be acceptable and recommends approval of the modification.

1 INTRODUCTION

This memorandum documents the Division of Risk Management's (DRISK) final review of the proposed modification to the SSS Risk Evaluation and Mitigation Strategy (REMS) for the extended-release and long-acting (ER/LA) opioid analgesics, or 'ER/LA opioids', initially received between June 9-13, 2014, and amended with the final documents between August 4, 2014 and August 13, 2014.

The proposed ER/LA REMS modification is to align the REMS with the safety labeling changes (SLC) approved on April 16, 2014. The labeling changes affected the indication,

[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.

[2] Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics; FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics, including Specific Drug information for ER/LA Opioid Analgesic Products; Prescriber Letter 1 (announcement of ER/LA REMS); Prescriber Letter 2 (announcement of REMS CE training); Prescriber Letter 3 (for newly registered DEA prescribers); Professional Organization/Licensing Board Letter 1(announcement of ER/LA REMS); Professional Organization/Licensing Board Letter 2 (announcement of REMS CE training); and, ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com) including the landing page and the webpage listing covered products under the REMS program.

limitations of use, warnings and precautions, and other sections - including an addition to the boxed warning about the risk of NOWS. The ER/LA REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), and a timetable for submission of assessments of the REMS. The modification impacts the REMS document, appended materials, and REMS Supporting Document (SD).

1.1 BACKGROUND

The ER/LA Opioid Analgesics REMS (ER/LA REMS) includes ER/LA opioid brand name and generic products formulated with the active ingredients: buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, hydrocodone, and tapentadol. ER/LA opioids are approved for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Although, all opioid formulations have the potential for misuse, abuse, overdose and death, the Agency believes that ER/LA opioids possess a significant safety concern because they contain more opioid per tablet, capsule, or patch, and either stay in the body longer or are released into the body over longer periods of time. Additionally, when the extended-release features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an immediate-release manner, potentially resulting in overdose.

As described in DRISK's July 6, 2012 Final REMS review, in accordance with section 505-1 of the FDCA, the Agency determined that a REMS is necessary for ER/LA opioids to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. Additionally, in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a SSS should be used to implement the REMS for all members of the class.

The ER/LA REMS is a SSS and was originally approved on July 9, 2012. The manufacturers of ER/LA opioids are collectively referred to as the REMS Program Companies (RPC). Modifications to the ER/LA Opioid Analgesic REMS were approved on August 28, 2012 and April 15, 2013.

The goal of the ER/LA 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 REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), and a timetable for submission of assessments of the REMS.

The ETASU includes a training program for prescribers that is not linked to restricted distribution. The tools used to support the ETASU include continuing education (CE) programs by CE providers on the safe use of ER/LA opioids, letters for prescribers and professional organizations to inform them about the program, a patient counseling document, and a REMS website. The timetable for submission of assessments is at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter.

1.2 REGULATORY HISTORY

Following is an overview of the regulatory history for the proposed ER/LA REMS Modification:

September 10, 2013: A SLC and post marketing requirements notification letter was sent to the NDA holders and ANDA holders (whose products are the reference listed drugs) of all ER/LA opioid products. The revised label information noted that ER/LA opioids 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. Because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, the new labels contain limitations of use statements reminding prescribers that these drugs are to be used only in patients for whom alternative treatment options are ineffective, not tolerated, or inadequate in providing sufficient pain management. Further, the labels state that ER/LA opioids are not indicated for "as-needed" pain relief.

FDA also modified the boxed warning in the labels for the ER/LA opioids to include the risk of NOWS, following chronic use of these products during pregnancy. NOWS may be life-threatening and requires management according to protocols developed by neonatology experts.

Along with the revised indication and the addition of the risk of NOWS to the boxed warning, ER/LA opioid application holders were notified of the need for safety labeling changes to the following label sections: Dosage and Administration, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Patient Counseling Information, and the Medication Guide. The application holders were informed of these specific safety label changes in the safety labeling change and post marketing requirements notification letter.

October 25, 2013: FDA approved Zohydro ER (hydrocodone bitartrate extended-release capsules) for the management of pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatment options are inadequate. Zohydro ER, a Schedule II controlled substance under the Controlled Substances Act, is the first FDA-approved single-entity (not combined with an analgesic such as acetaminophen) extended- release hydrocodone product. Zohydro ER was approved as a member of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS).

April 16, 2014: FDA issued a SLC Approval Letter/ REMS Modification Notification letter approving SLCs for Sponsors of ER/LA opioids NDAs and ANDAs whose referenced NDAs are no longer marketed. The labeling changes affected the indication, limitations of use, warnings and precautions, and other sections - including an addition to the boxed warning about the risk of NOWS.

These letters also notified the Sponsors of the requirement to modify the ER/LA REMS to reflect the newly approved labeling changes. It requested each Sponsor submit a proposed REMS modification to their respective application in order to reflect the recent

SLC and to ensure all members of the SSS were approved with the current version of the REMS.

April 23, 2014: The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sent an email to the RPC, containing the following Agency-modified REMS materials to reflect the approved SLC: REMS Document, Patient Counseling Document, FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics, Dear DEA-Registered Prescriber Letters, Dear [Licensing Board/Association] Letters, ER/LA Opioid REMS website, and the REMS SD.

To streamline the review process for subsequent rounds of revisions, FDA advised the RPC sponsors to work together to create one set of shared documents, and e-mail the shared documents, on behalf of all the participating ER/LA sponsors, to the Agency prior to submitting to individual applications.

May 29, 2014: DAAAP sent a Prior Approval Supplement Request/REMS Modification Notification Letter to Zogenix, Inc. for Zohydro ER, informing the Sponsor that the label for Zohydro needed to align with the SLC approved for the ER/LA opioids class. Although the originally approved labeling for Zohydro ER contained most of the safety labeling language approved on April 16, 2014, some language was modified during the review of the class supplements. The Sponsor was also notified that a proposed REMS modification should be submitted.

June 9, 2014 - June 13, 2014: Individual Sponsors submitted the RPC agreed upon, proposed modified ER/LA REMS to their respective applications. Please see the table of submissions on page one for the exact dates of each submission.

June 30, 2014: FDA approved a Prior Approval Supplement for Butrans which authorized the addition of a new dosage strength (7.5 mcg/hour). The ER/LA REMS was modified to add this new strength to the ER/LA REMS Blueprint. DRISK completed a final review of the REMS on June 24, 2014.

July 23, 2014: FDA approved Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), for oral use, CII for the management of pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatment options are inadequate. DRISK completed a final review of the modified REMS on July 23, 2014.

July 24, 2014: The Agency sent via email revised REMS materials reflecting: the safety label changes approved on April 16, 2014, the addition of Zohydro and Targiniq, plus the addition of the new dosage strength for Butrans.

August 18, 2014: DRISK provided the RPC with final REMS documents and submission instructions for each applicant to submit to their respective NDAs/ANDAs.

August 4 -13, 2014: All RPC sponsors submitted their final ER/LA REMS to their respective applications. Please see the table of submissions on page one for the exact dates of each submission.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

Please see the table on page one of this review for a complete list of submissions for this REMS Modification.

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Rappaport B, Hertz S, Fields, E. DAAAP SLC Review/FDA Response to Citizen Petition, September 6, 2013.
- FDA SLC Notification Letter for ER/LA Opioids, September 10, 2013.
- Smith D. DRISK Zohydro REMS Review, September 23, 2013.
- Fuller B. PLT Review for Medication Guides and Instructions for Use for ER/LA Opioid Class Products, March 21, 2014.
- E. Chung-Davies. OPDP Review for ER/LA REMS Materials, April 7, 2014.
- FDA SLC Approval/ REMS Modification Notification Letter for ER/LA Opioids. April 16, 2014.
- Email to RPC with revised ER/LA REMS materials, April 23, 2014.
- FDA PAS Request and REMS Modification Notification Letter for Zohydro, May 29, 2014.
- Lehrfeld K. DRISK Butrans REMS Review, June 30, 2014.
- Lehrfeld K. DRISK Targiniq REMS Review, July 23, 2014.

3 RESULTS OF REVIEW OF PROPOSED ER/LA REMS MODIFICATION

3.1 RATIONALE FOR THE PROPOSED REMS MODIFICATION

On September 10, 2013, FDA announced class-wide safety labeling changes and new post-market study requirements for all ER/LA opioids intended to treat pain. On April 16, 2014, FDA approved the SLC for Sponsors of ER/LA opioids NDAs and ANDAs whose referenced NDAs are no longer marketed. The proposed SLC impacted the ER/LA REMS materials.

When the Agency approves SLCs, regulations (Sec 505-1. [355-1] (h)(2)(A)(iii)[3]) require that FDA must approve the REMS modification within 60 days of the REMS modification being submitted.

[3] Sec 505-1. [355-1] (h)(2)(A)(iii) REMS Modification Due to Safety Label Changes.- Not later than 60 days after the Secretary receives a proposed modification to an approved risk evaluation and mitigation strategy to conform the strategy to approved safety label changes, including safety labeling changes initiated by the sponsor in accordance with FDA regulatory requirements, or to a safety label change that the Secretary has directed the holder of the application to make pursuant to section 355(o)(4) of this title, the Secretary shall review and act on such proposed modification to the approved strategy.

The purpose of the current REMS modification was the following:

- Include revisions necessary to align the ER/LA REMS materials with the approved SLCs for all Sponsors of ER/LA opioids;
- Include the addition of Zohydro ER and Targiniq in the ER/LA REMS for all the RPC Sponsors as this is the first modification by all the RPC Sponsors after the approval of two products; and
- Include the addition of the Butrans 7.5 mcg/hr dosage strength in the ER/LA for all the RPC Sponsors as this is the first modification by all the RPC Sponsors after the PAS approval for the new dosage strength.

3.2 PROPOSED REMS MODIFICATIONS

The proposed modifications to the REMS elements are described below. Added or revised text is noted by underline.

3.2.1 Goals

No changes to the goals of the REMS are included in this modification.

3.2.2 REMS Elements

3.2.2.1 Medication Guide

NDA/ANDA holders proposed changes to the Medication Guides to align with the FDA required SLC. These changes were reviewed under separate cover by Office of Medical Policy/Patient Labeling Team, dated March 21, 2014.

3.2.2.2 Elements to Assure Safe Use

3.2.2.2.1 REMS Document

The following modifications for ER/LA Opioid Analgesic REMS were proposed:

Subsection I.B.1.a.3) was revised to: "…it includes a ~~post course~~ knowledge assessment of all of the sections of the FDA Blueprint."

Subsection 1.B d. ii 2. was revised to: "…whether the ~~post course~~ knowledge assessment measures..."

Reviewer Comment: The word "post-course" was deleted as the knowledge assessments may take place any time during the training program.

3.2.2.2.2 REMS Appended Material

A. Patient Counseling Document (PCD) on ER/LA Opioid Analgesics

The fourth bullet of the "DON'T" section was changed to: "**Do not** cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider."

Reviewer Comment: These changes were made to ensure consistency with the safety label

changes in all ER/LA opioid products.

The second bullet in the **"Take this card with you…."** section was added stating, "if you are pregnant or planning to become pregnant."

Reviewer Comment: These additions were made to highlight the new safety labeling changes related to pregnancy and NOWS.

B. FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics

In the section titled, **Why Prescriber Education is Important**, the following sentence was added to the 2nd paragraph: "ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain."

In Section I, **Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy** subsections a., i. through viii were edited as follows:

i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.
ii. Life-threatening respiratory depression
iii. Abuse by patient or household contacts.
iv. Misuse and addiction.
v. Physical dependence and tolerance.
vi. Interactions with other medications and substances (See table in Section VI for specific information).
vii. Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy.
viii. Inadvertent exposure/ingestion by household contacts, especially children.

In Section I, **Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy** subsection b., i. was edited as follows:

i. Obtain a complete history and conduct a complete physical examination. The history should include assessment for a family history of substance abuse and psychiatric disorders, as well as special considerations regarding dose and adverse effects in geriatric patients, pregnant women, ~~and the elderly~~ and children.

In Section II, **Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics** subsection b., ii., the following text was added:

> Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients. Opioid-tolerance is defined as follows: patients receiving, for one week or longer, 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.

In Section II, **Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics** subsection g., the text was revised as follows:

Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids and monitor patients closely, especially at the time of treatment initiation and dose increases.

In Section III, **Managing Therapy with ER/LA Opioid Analgesics**, the following text was added:

e. Prescribers should be aware that there are no adequate and well-controlled studies of ER/LA opioid analgesics in pregnant women. ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

f. Prescribers should be aware of the pregnancy status of their patients. If opioid use is required for a prolonged period in a pregnant woman, prescribers should advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

In Section IV, **Counselling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics**, sub points j and r were revised as follows:

j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended. 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.

r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf *(this website URL was updated)*

In Section V, **General Drug Information for ER/LA Opioid Analgesics**, sub point h. was added:

Follow the instructions for conversion in the Dosage and Administration section (2.1) in the Prescribing Information of each product when converting patients from one opioid to another.

In Section VI, Specific Drug Information for ER/LA Opioid Analgesics, were edited as noted on Appendix A, in which the following charts are placed with all changes noted. This also includes the addition of drug specific information for Zohydro and Targiniq.

- Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics
- Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

Reviewer Comment: The previous additions and revisions were made to the FDA Blueprint to ensure consistency with the new safety labeling changes. The RPC accepted all revisions to the FDA Blueprint as requested in the REMS Modification Notification email on April 23, 2014.

Office of Prescription Drug Promotion (OPDP) was consulted on January 24, 2014 and submitted a review of the ER/LA REMS materials on March 27, 2014. Their review was entered into DARRTS on April 7, 2014. Most of their recommendations were accepted. However, after further discussion and in consultation with DAAAP, DRISK did not accept the following comments as they related to Section VI in the FDA Blueprint. The reason is noted after each comment.

- "Section VI. Specific Drug Information for ER/LA Opioid Analgesic Products includes a table entitled, "Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics). In the first row listing all of the affected products, we note that Palladone has not been listed. Please consider adding information regarding Palladone, if appropriate."

  DRISK did not accept "consider adding information regarding Palladone, if appropriate" because the NDA for Palladone has been withdrawn.

- "In order to maintain consistency among the competitor products and to avoid implications of superiority, we recommend deleting all references to the trade name (for example, page 7 of the blueprint refers to "OxyContin") and replacing it with "ER/LA opioid products" or similar."

  DRISK did not accept "*deleting all references to the trade name..."* because all ER/LA opioids are listed equally, it is safer to distinguish their differences as separate molecular entities, and they are referred to by their trade names throughout the REMS materials.

C. Prescriber Letters 1, 2, and 3 and Professional Organization/ Licensing Board Letters 1 and 2

The following text was added to the top of each respective letter in a box to indicate that these letters were no longer being distributed.

- Prescriber Letter 1: <u>This letter ceased distribution on 7/31/12</u>
- Prescriber Letter 2: <u>This letter ceased distribution on 1/28/13</u>
- Professional Organization/Licensing Board Letter 1: <u>This letter ceased distribution on 8/24/12</u>
- Professional Organization/Licensing Board Letter 2: <u>This letter ceased distribution on 1/24/13</u>

<u>Reviewer Comment:</u> *The date of cessation of distribution of the letter was added to REMS materials. FDA recommended making these additions since these materials are no longer applicable to stakeholders and contain historic information only.*

The following text was added to Prescriber Letter 3, which is intended for newly DEA registered prescribers and is required by the ER/LA REMS to be mailed out monthly. This text was inserted after the first paragraph. The third paragraph as noted below was deleted.

> <u>ER/LA opioid analgesics are used for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which</u>

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

They 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.

~~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.~~

Reviewer Comment: Additional text was added to Prescriber Letter #3 to align with the new SLC.

The word "post-course" was deleted from the first bullet entitled **Train (Educate Yourself)**, item (c) "include a ~~post course~~ knowledge assessment…"

Reviewer Comment: The word "post-course" was deleted as the knowledge assessments may take place any time during the CE program.

OPDP was consulted on January 24, 2014 and submitted a review of the ER/LA REMS materials on March 27, 2014. Their review was entered into DARRTS on April 7, 2014. Most of their recommendations were accepted. However, after further discussion and in consultation with DAAAP, DRISK did not accept the following comments as they related to letters for prescribers, professional organizations, and licensing boards. The reason is noted after each comment.

- "Prescriber Letters 1, 2, and 3 & Professional Organization/Licensing Board Letters 1 and 2: We note that the full indications are not presented in the letters. We acknowledge that the previously approved letters did not include the full indications. However, given that these letters will be communicated following the Safety Labeling Change supplement approvals which include revised indications, we recommend that the letters be revised to include the full approved indication, including limitations.

  We are concerned that the proposed letters each substantially minimize the risks associated with ER/ER Opioid products by failing to adequately communicate specific important information that is material as outlined in the Boxed Warning and Warnings sections of the PIs (e.g., life-threatening respiratory depression, fatal drug interactions) regarding the serious REMS risks associated with inappropriate prescribing, misuse, and abuse. Although we acknowledge that the PCD will accompany Prescriber Letters 1 and 3 and Professional Organization/Licensing Board Letter 1, along with the link to the

www.ER-LA-opioidREMS.com website in all of the letters, we recommend outlining specific REMS related risk in the letters. We would not object to the inclusion of "Selected Important Safety Information" similar to the approved TIRF REMS Access Program: "Dear Healthcare Provider Letter."

DRISK did not accept "that the letters be revised to include the full approved indication, including limitations" or "outlining specific REMS related risk in the letters" for the following reasons:

- Only the Prescriber Letter 3 (for newly registered DEA prescribers) will continue to be distributed. The remaining letters are no longer distributed.
- The primary purpose of Prescriber Letter 3 is to announce the ER/LA REMS and to notify likely prescribers of the CE training opportunities - where they will receive the necessary information to safely prescribe ER/LA Opioid REMS drugs. It also references the ER/LA Opioid REMS website for additional information.

D. REMS Website (www.ER-LA-opioidREMS.com)

The following represents modifications to the REMS website:

a) A pop-up notice summarizing the SLC will appear when the home page of the ER/LA REMS website is opened. It will read:

IMPORTANT SAFETY LABEL CHANGES!

Revised Indication

For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Revised Warnings

ADDICTION, ABUSE and MISUSE

LIFE-THREATENING RESPIRATORY DEPRESSION

ACCIDENTAL INGESTION

CYTOCHROME P450 3A4 INTERACTION.

New Warning

NEONATAL OPIOID WITHDRAWAL SYNDROME

Please click on the U.S. Prescribing Information link (make this an active hyperlink) for the complete label for each ER/LA opioid drug.

b) The banner "Looking for Accredited REMS CME/CE? Click Here." was added to all pages on the website.
c) Under Materials for Healthcare Professionals, the link entitled, Dear DEA-Registered Prescriber Letters was change to the singular form.
d) "About Us" added as a link to all pages of the website.
e) The website feature "Last updated Month, Day, Year" was added to all pages of the website.

f) On the 2nd page of the website entitled, **REMS-Compliant CE for ER/LA Opioid Analgesics** the 2nd paragraph was edited to delete the word, "~~post-course~~" in item c).

g) On the page that lists the **Dear DEA-Registered Prescriber Letter~~s~~**, the title of the link was change to the singular form and links to the following letters were removed:

- Dear DEA-Registered Prescriber Letter 1 - Announcing REMS approval
- Dear DEA-Registered Prescriber Letter 2 - Announcing REMS-related CME/CE opportunities

h) The **Selected Important Safety Information** was changed as follows:

The following text was added/deleted as follows:

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. **ER/LA opioid analgesics are not indicated for acute pain**.

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

Additionally, ER hydromorphone and transdermal fentanyl products are only indicated for use in opioid-tolerant patients. 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.

After the paragraph starting with **"Transdermal dosage forms…",** the following text was inserted:

As stated in the ~~revised~~ Boxed Warning, prescribers need to be aware of the following:

- ER/LA Opioid Analgesics exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions.

- Serious life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ER/LA Opioid Analgesics tablets whole to avoid exposure/ingestion to a potentially fatal dose.

- Accidental ingestion of ER/LA Opioid Analgesics, especially in children, can result in fatal overdose.

- Prolonged use of ER/LA Opioid Analgesics during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

- Initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose.

i) Under the section **Adverse Reactions**, text in the 2nd paragraph was revised as follows:

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

j) Under the section **Adverse Event Reporting**, the third bullet was revised to provide an updated location for the pdf FDA Form 3500 as follows:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf

Reviewer Comment: All changes to the ER/LA REMS website were made to ensure consistency with the approved SLC for ER/LA opioids.

OPDP was consulted on January 24, 2014 and submitted a review of the ER/LA REMS materials on March 27, 2014. Their review was entered into DARRTS on April 7, 2014. Most of their recommendations were accepted. However, after further discussion and in consultation with DAAAP, DRISK did not accept the following comments as they related to the ER/LA REMS website. The reason is noted after each comment.

- "We note that the goal of the REMS is not presented. We acknowledge that the definition of REMS is presented as well as the core messages from the blueprint; however, this is not sufficient. We recommend that the goal of the REMS specific to the ER/LA opioid products is clearly communicated."

DRISK did not accept "that the goal of the REMS specific to the ER/LA opioid products is clearly communicated" on the website because we no longer state the actual goals of the REMS on all websites. Goals are written in the REMS document in a way that the program can be assessed, not for the purposes of the target audience.

- "We recommend inclusion of the risk regarding the drug interaction with alcohol. We acknowledge that only 5 of the ER/LA products include this specific risk in the Boxed Warning; however, we recommend inclusion due to its relevance to the REMS related risk and its potentially fatal consequences."

DRISK did not accept "that inclusion of the risk regarding the drug interaction with alcohol" be included on the ER/LA REMS website. ER/LA opioid interactions with alcohol are mentioned over 20 times throughout the REMS materials. The review division was consulted and agreed with DRISK's recommendation on this matter.

3.2.3 Timetable for Submission of Assessments

The Timetable for submission of assessments was revised to remove the requirement for the ANDA holders to submit assessments.

3.3 REMS ASSESSMENT PLAN

Based on the proposed modifications, the REMS assessment plan has not changed; the REMS assessment plan will remain the same as that described in the July 9, 2012 Approval letter.

3.4 REMS SUPPORTING DOCUMENT

The NDA/ANDA holders proposed a revision the SD by adding Table 2 to the Table of Contents.

Reviewer Comments: Table 2 in the Table of Contents was inadvertently deleted from the REMS SD at the time of initial REMS approval. The proposed revision is acceptable.

The NDA/ANDA holders proposed revisions to the SD to describe changes to the ER/LA REMS call center, which was transitioned to an interactive voice mail/message retrieval system in XXXX.

Reviewer Comments: This revision was agreed to by the Agency and is acceptable.

Based on communications with providers and a major accrediting body, the RPC has come to understand that it is not necessary to approach the Long-Term Evaluation with a process similar to that for continuing education grants. The RFP process proposed here will allow the RPC to provide input into the Long-Term Evaluation protocol and other aspects of the assessment. RPC communicated this position to FDA on 1/21/2014. FDA responded on 2/11/2014 and stated: "Revisions to the Supporting Document to reflect the

current process for obtaining agreements between the RPC and vendors for the long term evaluation assessments are necessary."

Reviewer Comments: This revision is acceptable.

4 DISCUSSION AND CONCLUSION

DRISK finds the proposed REMS modification for the ER/LA Opioid Analgesics REMS as submitted between August 4-13, 2014 acceptable. 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 Analgesic REMS is acceptable to the Office of Surveillance and Epidemiology (OSE), Office of Medication Error and Prevention and Risk Management (OMEPRM), DRISK.

5 RECOMMENDATIONS

The OSE, OMEPRM, DRISK recommends approval of the REMS Modification for ER/LA Opioid Analgesic REMS received August 4-13, 2014 and appended to this review.

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

The following websites must be updated with the REMS appended to this review:

- Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids, Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm
- Approved Risk Evaluation and Mitigation Strategies (REMS), Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm
    - Website must also be updated to include the "List of Approved Application Numbers and Sponsors"

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. Appendix A (updated common and drug specific information to reflect SLCs):
    a. Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics
    b. Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)
5. Prescriber Letter 1
6. Prescriber Letter 2
7. Prescriber Letter 3

8. Professional Organization/Licensing Board Letter 1
9. Professional Organization/Licensing Board Letter 2
10. ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com), including the landing page, the webpage listing covered products under the REMS program.

Appendix A

Please note: Additions are noted as underlined text. Deleted text is ~~crossed through~~.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
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 ~~C~~ER tablets) Tablets **Zohydro ER** (hydrocodone bitartrate ER capsules)	**Butrans** (buprenorphine transdermal system) **Duragesic** (fentanyl transdermal system) **Exalgo** (hydromorphone HCl ER tablets) **MS Contin** (morphine sulfate ~~C~~ER tablets) **Opana ER** (oxymorphone HCl ER tablets) **Targiniq ER** (oxycodone HCl/naloxone HCl) ER
Dosing Interval	▪ Refer to individual product information.
Key Instructions	▪ Limitations of usage: • Reserve for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • 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. ▪ 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.~~ ~~• 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: • 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: • 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.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Interactions Common to the Class	▪ 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. ▪ Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and butorphanol) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. ~~▪ 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.~~ ▪ 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	▪ Patients considered opioid tolerant are those receiving, for one week or longer: ▪ 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 ▪ See individual product information for which products: • 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	▪ 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) See individual product information for additional contraindications.
Relative Potency To Oral Morphine	▪ **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	▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate in increments of not greater than 30 mg using a minimum of 3 to 4 day intervals ~~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	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp~~GP~~ 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, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	▪ 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 in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10 mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20mcg/hour ~~adjustment.~~ ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application • 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	▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III ~~antiarrythmics~~ antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and
Use in Opioid-Tolerant Patients	Butrans 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for use in opioid- tolerant patients only.
Drug-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	Every 8 to 12 hours
Key Instructions	▪ 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. ▪ Dosage adjustments may be done using a minimum of 1 to 2 day intervals. ▪ 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	▪ Pharmacokinetic drug-drug interactions with methadone are complex. ▪ 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	▪ 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	▪ 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 • 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 a minimum of ~~noless than~~ 72 hour intervals between dose adjustments. • 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. **Specific contraindications:** ▪ 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	▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure. • Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Use in Opioid-Tolerant Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ 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	▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 1 to 2 day intervals ~~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	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp ~~GP~~ 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	▪ 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 in increments of 4 to 8 mg using a minimum of 3 to 4 day intervals ~~using a minimum of 3 to 4 day intervals.~~ ▪ Swallow tablets whole (do not chew, crush, or dissolve).
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	▪ 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)

	▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp ~~GP~~ 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~~ Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp ~~GP~~ 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	▪ 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	▪ 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	▪ 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	▪ 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)	
	▪ Titrate in increments of 5 to 10 mg ~~every 12 hours~~ using a minimum of 3 to 7~~2~~-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.

Specific Drug Interactions	▪ 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	▪ Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	▪ Oxycodone Hydrochloride ▪ ~~Controlled~~ Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ ~~Opioid naïve patients: Initiate treatment~~ Initial dose in opioid non-tolerant patients is ~~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).
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant	▪ 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	▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Zohydro ER	▪ Hydrocodone Bitartrate ▪ Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate in increments of 10 mg ~~every 12 hours~~ using a minimum of 3 to 7day intervals. ▪ ~~Swallow capsules whole (do not chew, crush, or dissolve)~~
Specific Drug Interactions	▪ 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	▪ 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.
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.	
Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-release tablets, 10/5 mg, 20/10 mg, and 40/20 mg
Dosing Interval	Every 12 hours

Key Instructions	• Opioid-naïve patients: initiate treatment with 10 / 5 mg every 12 hours. • Titrate using a minimum of 1 to 2 day intervals. • Do not exceed 80 / 40 mg total daily dose (40 /20 mg q12) of Targiniq ER • May be taken with or without food. • Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. • Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild 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.
Specific Drug Interactions	• CYP3A4 inhibitors may increase oxycodone exposure. • CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid-Tolerant Patients	• Single dose greater than 40/20 mg or total daily dose of 80/40 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	• Contraindicated in patients with moderate to severe hepatic impairment.
Relative Potency To Oral Morphine	• See individual product information for conversion recommendations from prior opioid.

Initial REMS Approval: 07/2012
Most Recent Modification: 08/2014

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 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 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.

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

Patient Name:

The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics

DO:

- Read the **Medication Guide**
- Take your medicine exactly as prescribed
- Store your medicine away from children and in a safe place
- Flush unused medicine down the toilet
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Call 911 or your local emergency service right away if:

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

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

DON'T:

- **Do not** give your medicine to others
- **Do not** take medicine unless it was prescribed for you
- **Do not** stop taking your medicine without talking to your healthcare provider
- **Do not** cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to: **dailymed.nlm.nih.gov**

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

Patient Name:

Patient Specific Information

Take this card with you every time you see your healthcare provider and tell him/her:

- Your complete medical and family history, including any history of substance abuse or mental illness
- If you are pregnant or are planning to become pregnant
- The cause, severity, and nature of your pain
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

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.

[1]Accreditation Council for Continuing Medical Education. 2014. *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria.* Accessed on May 24, 2014.
[2]Accreditation Council for Continuing Medical Education. 2014. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support.* Accessed on May 24, 2014.

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. ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

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.

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[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 May 24, 2014.

[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 May 24, 2014.

[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 May 24, 2014.

ii. Life-threatening respiratory depression
iii. Abuse by patient or household contacts.
iv. Misuse and addiction.
v. Physical dependence and tolerance.
vi. Interactions with other medications and substances (See table in Section VI for specific information).
vii. Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy.
viii. Inadvertent exposure/ingestion 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. The history should include assessment for a family history of substance abuse and psychiatric disorders, as well as special considerations regarding dose and adverse effects in geriatric patients, pregnant women, 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. **Opioid-tolerance is defined as follows:** patients receiving, for one week or longer, 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.
   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 and monitor patients closely, especially at the time of treatment initiation and dose increases
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 should be aware that there are no adequate and well-controlled studies of ER/LA opioid analgesics in pregnant women. ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
f. Prescribers should be aware of the pregnancy status of their patients. If opioid use is required for a prolonged period in a pregnant woman, prescribers should advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
g. 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.
h. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
i. 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, even when used as recommended. 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/AboutFDA/ReportsManualsForms/Forms/UCM163919.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.
h. Follow the instructions for conversion in the Dosage and Administration section (2.1) in the *Prescribing Information* of each product when converting patients from one opioid to another.

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)	
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 ER tablets) **Zohydro ER** (hydrocodone bitartrate ER capsules)	**Butrans** (buprenorphine transdermal system) **Duragesic** (fentanyl transdermal system) **Exalgo** (hydromorphone HCl ER tablets) **MS Contin** (morphine sulfate ER tablets) **Opana ER** (oxymorphone HCl ER tablets) **Targiniq ER** (oxycodone HCl/naloxone HCl ER tablets)
Dosing Interval	▪ Refer to individual product information.
Key Instructions	▪ Limitations of usage: • Reserve for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • 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. ▪ 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.** ▪ Solid oral dosage forms: • 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: • 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: • Dosage reduction for hepatic or renal impairment.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Interactions Common to the Class	▪ 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. ▪ Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and butorphanol) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. ▪ 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	▪ Patients considered opioid tolerant are those receiving, for one week or longer: ▪ 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 ▪ See individual product information for which products: • 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	▪ 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) See individual product information for additional contraindications.
Relative Potency To Oral Morphine	▪ **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	▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate in increments of not greater than 30 mg using a minimum of 3 to 4 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	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp 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, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	▪ 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 in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20mcg/hour ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application • 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	▪ 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 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for use in opioid- tolerant patients only.
Drug-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	Every 8 to 12 hours
Key Instructions	▪ 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. ▪ Dosage adjustments may be done using a minimum of 1 to 2 day intervals. ▪ 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	▪ Pharmacokinetic drug-drug interactions with methadone are complex. ▪ 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	▪ 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	▪ 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 • 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 a minimum of 72 hour intervals between dose adjustments. • 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. **Specific contraindications:** ▪ 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	▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure. ▪ Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Use in Opioid-Tolerant Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ 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	▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 1 to 2 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	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp 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	▪ 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 in increments of 4 to 8 mg 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	▪ 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)	
	▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp 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 Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp 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	▪ 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	▪ 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	▪ 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	▪ 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)	
	▪ Titrate in increments of 5 to 10 mg using a minimum of 3 to 7-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	▪ 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	▪ Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	Oxycodone Hydrochloride Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patients is 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	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	▪ 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	▪ 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.
Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12) of Targiniq ER ▪ May be taken with or without food. ▪ Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. ▪ Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild 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.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid-Tolerant Patients	▪ Single dose greater than 40 mg/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Product-Specific Safety Concerns	▪ Contraindicated in patients with moderate to severe hepatic impairment.
Relative Potency To Oral Morphine	▪ See individual product information for conversion recommendations from prior opioid.
Zohydro ER	Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate in increments of 10 mg using a minimum of 3 to 7day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	▪ 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	▪ 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.
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.	

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.

- **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

This letter ceased distribution on January 28, 2013

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 analgesics[1] 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.

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**

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

They 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 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.
- **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 includes 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

This letter ceased distribution on August 24, 2012

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.

- **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/ingestion,
- 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 analgesics[1] 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/AboutFDA/ReportsManualsForms/Forms/UCM163919.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.

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

Looking for Accredited REMS CME/CE? Click Here.

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.

Accredited Continuing Education for Healthcare Professionals

REMS-Compliant CE for ER/LA Opioid Analgesics

Listing of Accredited CME/CE REMS-Compliant Activities Supported by RPC *UPDATED*

Continuing Education Provider Information

Materials for Healthcare Professionals

Dear DEA-Registered Prescriber Letter

Patient Counseling Document

Medication Guides

Healthcare Professional Frequently Asked Questions

Materials for Patients

Medication Guides

Patient Frequently Asked Questions

Get ADOBE READER

Last Updated: Month Day, Year

Looking for Accredited REMS CME/CE? Click Here.

REMS-Compliant CE for ER/LA Opioid Analgesics

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 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

Listing of Accredited CME/CE REMS-Compliant Activities Supported by RPC *UPDATED*

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

If you are a CE provider, click here for more information

Last Updated: Month Day, Year

Looking for Accredited REMS CME/CE? Click Here.

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) - English

Patient Counseling Document (PCD) - Spanish

PCD Order Form

Last Updated: Month Day, Year

Looking for Accredited REMS CME/CE? Click Here.

Dear DEA-Registered Prescriber Letter

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

- Dear DEA-Registered Prescriber Letter 3 - Announcing REMS approval and REMS-related CME/CE opportunities to newly DEA-registered Schedule II and III Prescribers

Last Updated: Month Day, Year

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

Looking for Accredited REMS CME/CE? Click Here.

Products covered under the ER/LA Opioid Analgesics REMS Program

Brand Name Products

Trade Name	Generic Name	Company	Contact	Links

BACK TO TOP

Generic Name Products

Trade Name	Generic Name	Company	Contact	Links

BACK TO TOP

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.

Last Updated: Month Day, Year

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 pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. **ER/LA opioid analgesics are not indicated for acute pain.**

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

As stated in the **Boxed Warning**, prescribers need to be aware of the following:

- **ER/LA Opioid Analgesics exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions.**

- **Serious life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ER/LA Opioid Analgesics tablets whole to avoid exposure/ingestion to a potentially fatal dose.**

- **Accidental ingestion of ER/LA Opioid Analgesics, especially in children, can result in fatal overdose.**

- **Prolonged use of ER/LA Opioid Analgesics during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**

- **Initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose.**

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/ingestion 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:

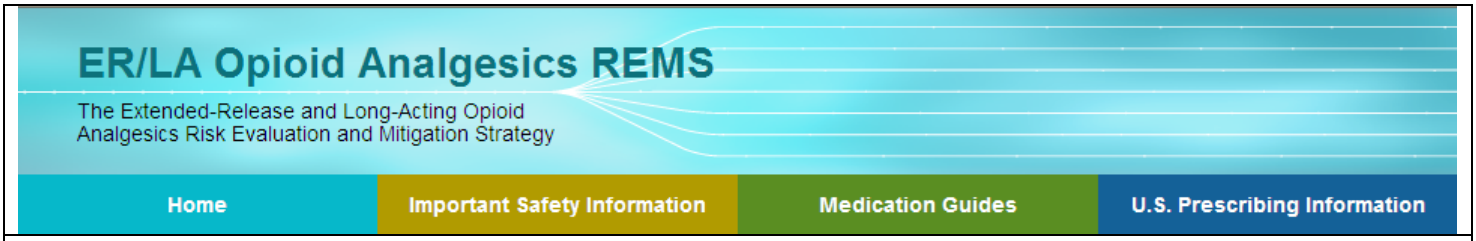
- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm *or*
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf

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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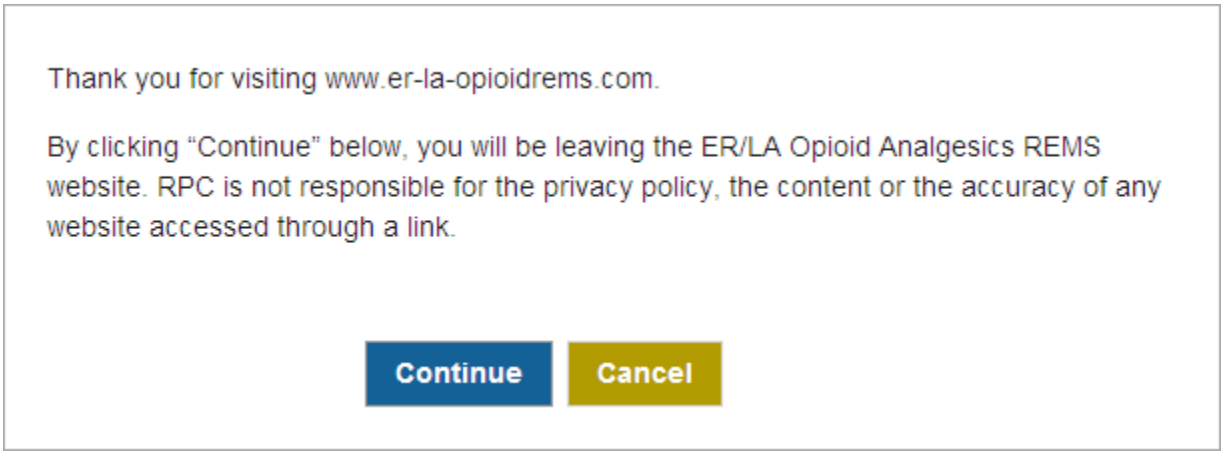
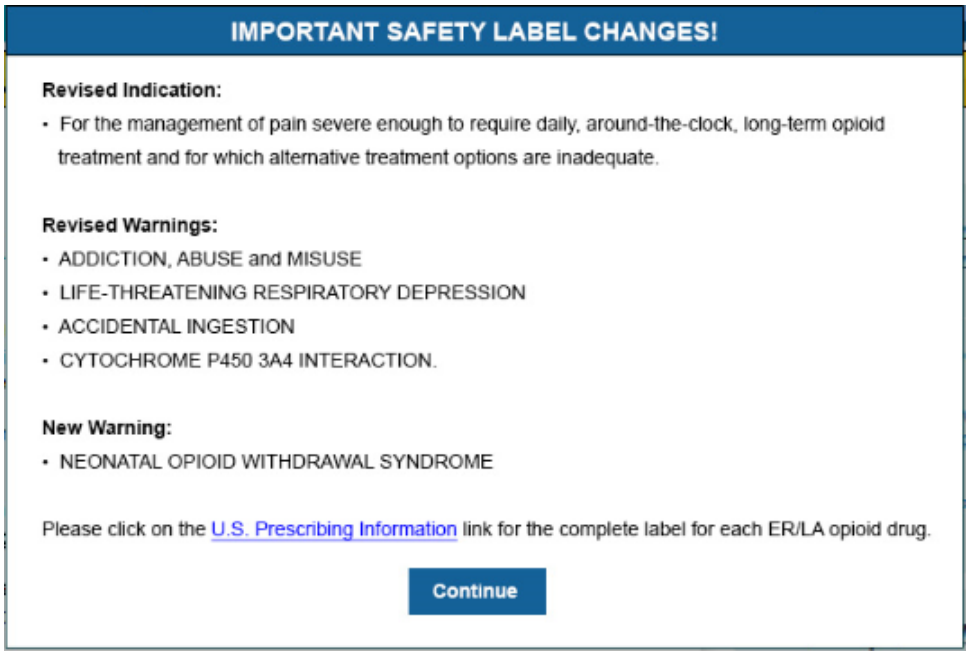
Interstitial Popup

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.



Safety Labeling Change Popup



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/s/

JOAN E BLAIR
08/18/2014

REEMA J MEHTA
08/18/2014