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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 6, 2012
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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	Applicant\ Sponsor	OSE RCM #	TSI #
AVINZA (morphine sulfate)	extended-release capsules	NDA 021260	0041	King	2011-1354	466
BUTRANS (buprenorphine)	transdermal system	NDA 021306	0079	Purdue	2011-1362	466 880
DOLOPHINE (methadone hydrochloride)	tablets	NDA 006134	0011	Roxane	2011-1368	466 254
Methadone	oral solution	ANDA 087997	0007	Roxane	--	--
Methadone	oral solution	ANDA 087393	0008	Roxane	--	--
Methadone	oral concentrate	ANDA 089897	0005	Roxane	--	--
DURAGESIC (Fentanyl Transdermal System)	transdermal system	NDA 019813	0072	Ortho-McNeil	2011-1357	466 392 255
EMBEDA (morphine	extended-release	NDA 022321	0064	Alpharma/King	2011-1346	466 1083

sulfate and naltrexone hydrochloride)	capsules					1135
EXALGO (hydromorphone HCl)	extended-release capsules	NDA 021217	0088	Mallinkrodt	2011-1356	466
KADIAN (morphine sulfate)	extended-release capsules	NDA 020616	0020	Actavis	2011-1344	466
MS CONTIN (morphine sulfate)	controlled-release tablets	NDA 019516	0023	Purdue	2011-1363	466
NUCYNTA ER (tapentadol)	extended-release oral tablets	NDA 200533	0065	Ortho-McNeil	2011-1361	466 926
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	0046	Endo	2011-1351	466
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 021610	0041	Endo	2011-1352	466
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 020553	0068	Purdue	2011-1364	466 1136
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 022272	0136	Purdue	2011-1366	466 1072

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EXECUTIVE SUMMARY

This memorandum documents the Division of Risk Management's (DRISK) final review of the following components of the proposed single-shared Risk Evaluation and Mitigation Strategy (REMS) for the class of extended-release and long-acting opioid analgesics, or 'ER/LA opioid analgesics'[1]: the REMS document, letters to health care providers and professional societies, website and select sections of the supporting document. The proposed single-shared ER/LA Opioid Analgesic REMS was agreed upon by FDA and the sponsors of ER/LA opioid analgesic products on June 7, 2012, and subsequently submitted by each sponsor to their individual applications over a seven day period, spanning from 13 June 2012 to 19 June 2012.

DRISK recommends to the multidisciplinary ER/LA Opioid REMS Small Steering Committee (SSC) and Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) approval of the components listed above, as part of the single-shared REMS for ER/LA opioid analgesics. The remaining REMS components were reviewed and/or developed by other offices within CDER, however, all final agreed upon REMS documents are appended to this review.

1 INTRODUCTION

1.1 BACKGROUND

Opioids have benefit when used properly and are a necessary component of pain management for certain patients. However, these products are associated with serious risks that can occur when used improperly including risk of addiction, high abuse potential, and severe psychological/physical dependence. In the past, FDA, drug manufacturers, and others have taken a number of steps to prevent misuse, abuse and accidental overdose of these drugs, including providing additional warnings in product labeling, implementing risk management plans, conducting inter-agency collaborations and issuing direct communications to both prescribers and patients. Despite these efforts, the rates of misuse, abuse, and accidental overdose of opioids, have risen and continue to be a major public health problem, which can result in fatal outcomes.

- 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.[2]

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

- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.[3]
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.[4]

Although, all opioid formulations have the potential for misuse, abuse, overdose and death, the Agency believes that ER/LA opioids are more of a safety concern than immediate-release opioid formulations because they contain more opioid per tablet, capsule or patch and either stay in the body longer or are released into the body over longer periods of time; and because, 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.

The REMS includes extended-release and long-acting opioid analgesic brand name and generic products formulated with the active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. ER/LA opioid analgesics 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.[5]

The ER/LA opioid analgesics include the following[6]:

NDA 021260	AVINZA (morphine sulfate) extended-release capsules
NDA 021306	BUTRANS (buprenorphine) Transdermal System for transdermal administration
NDA 006134	DOLOPHINE (methadone hydrochloride) tablets and its generic equivalents
ANDA 087997	Methadone Oral Solution and its generic equivalents
ANDA 087393	Methadone Oral Solution and its generic equivalents
ANDA 089897	Methadone Oral Concentrate
NDA 019813	DURAGESIC (Fentanyl Transdermal System) for transdermal administration and its generic equivalents
NDA 022321	EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules

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

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

[5] AVINZA, DOLOPHINE (pain indication only), EMBEDA, KADIAN, MS CONTIN, and OXYCONTIN share this same indication. The remaining products have similar indications with slight variations. However, DURAGESIC & EXALGO are specifically indicated for use in opioid tolerant patients.

[6] The ANDAs for select methadone products are listed because there is no corresponding reference listed NDA for these products.

NDA 021217	EXALGO (hydromorphone HCl) extended-release tablets
NDA 020616	KADIAN (morphine sulfate) extended-release capsules and its generic equivalent
NDA 019516	MS CONTIN (morphine sulfate) controlled-release tablets and its generic equivalents
NDA 200533	NUCYNTA ER (tapentadol) extended-release oral tablets
NDA 201655	OPANA ER (oxymorphone hydrochloride) extended-release tablets
NDA 021610	OPANA ER (oxymorphone hydrochloride) extended-release tablets and its generic equivalents
NDA 020553	OXYCONTIN (oxycodone hydrochloride) controlled-release tablets

1.2 REGULATORY HISTORY

In 2009, CDER formed a multi-office, executive-level small steering committee (SSC), known as the Opioid REMS SSC, to oversee and direct the design and review of the ER/LA Opioid Analgesic REMS. Details of the development and approval of the ER/LA Opioid Analgesic REMS are discussed in the Executive Memorandum, dated July 6, 2012; however, highlights are included below.

In February 2009, FDA notified sponsors of ER/LA opioid analgesics that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. Since that time, extensive internal discussion and numerous activities (involving over 100 FDA employees) were undertaken to support the development and implementation of a REMS for these products; activities included but were not limited to issuing Federal Register notices, holding a series of stakeholder, industry and public meetings, and holding a joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees.

After a comprehensive analysis of the public comments and advice received during these meetings, the Agency determined that the REMS elements would be implemented across the class of ER/LA opioid analgesics. In April of 2011, CDER sent letters to sponsors notifying them that, in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the Agency determined that a single-shared system should be used to implement the REMS for all products in the class. Further, sponsors were informed that the REMS must include the following goals and elements:

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

Medication Guide: The Medication Guide should have common content applicable to all ER/LA opioids, as well as product specific information that is necessary for safe and effective use of the drug.

Elements to Assure Safe Use: The REMS must include tools to manage these risks, including, at minimum, the following:

1. Ensure that training is provided to prescribers who prescribe ER/LA opioid analgesics. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to these drug products and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers.

2. Provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids.

3. Inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 6 months, 12 months, and annually after the REMS is initially approved.

In parallel with the Agency's extensive efforts, the manufacturers of ER/LA opioid analgesics formed a consortium that was ultimately referred to as the REMS Program Companies (RPC). The RPC met multiple times throughout the development and review of the REMS. Additionally, the RPC met periodically with the Agency to provide updates on their progress developing the single-shared ER/LA Opioid Analgesic REMS, and to obtain the Agency's feedback.

Between August 12 and August 17, 2011, the RPC's proposed, single-shared ER/LA Opioid Analgesic REMS was submitted by each of the applicants in the RPC to their respective, individual applications[7]. The submission contained the following documents: REMS Document, Medication Guide, Patient Medicine Information Sheet [currently known as the Patient Counseling Document], expanded outline of prescriber training program [currently known as the FDA Blueprint], Dear DEA-Registered Prescriber Letter, Dear [Licensing Board/Association] Letter, and REMS Supporting Document.

The review of the individual REMS materials were handled by multiple offices within CDER and all comments were provided to the SSC for clearance. The Offices/Divisions involved in the review of the REMS submission, and the materials that they were responsible for reviewing and revising are listed below:

[7] Each applicant submitted the same REMS proposal, but, as requested in the April 2011 REMS Notification letter, submitted a Medication Guide that contained both product-specific information and content common to all ER/LA opioid analgesics

- DRISK: REMS document, two letters[8], and the supporting document[9]
- Office of Medical Policy (OMP): Patient Counseling Document
- OMP with DAAAP: Medication Guides
- Office of the Center Director/Drug Safety Operations was responsible for drafting the FDA Blueprint and obtaining feedback from stakeholders and other federal agencies.

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.

Between August 2011 and June 2012, the FDA and RPC had at least 11 teleconferences to discuss revisions to the REMS documentation and materials. Following the initial submissions in August of 2011, the RPC submitted a revised proposal via email on January 12, February 3, March 6, March 23, April 9, April 16, May 11, May 29, June 5, and June 7, 2012.

On June 07, 2012, FDA determined that all required changes had been made, and requested that each sponsor submit the final agreed upon REMS to their respective NDAs and ANDAs. The submissions were received between June 13, 2012 and June 19, 2012.[10]

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The REMS proposal was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA); consistency with the REMS notification letters sent on February 6, 2009 and April 19, 2011; and the requirements FDA communicated to the RPC via e-mail and during teleconferences between August 2011 and June 2012.

2.2 ANALYSIS TECHNIQUES

DRISK's final review included the following submissions:

Drug Name	Application	Submission	FDA Receive Date

[8] Additional letters were added to the REMS over the course of the review (see Discussion Section)

[9] DRISK was responsible for reviewing the operational content of the supporting document; the Information Needed for Assessment of the REMS was developed by the SSC, with input from all members of the larger review team.

[10] Upon review of the first submissions received on 13 June 2012, an error was identified in the title on page 2 of the FDA Blueprint. Hence, sponsors that had not yet submitted were advised to make the correction prior to submitting, and note the correction in their cover letter. Sponsors that had submitted with the error were requested to submit a short letter as REMS correspondence, authorizing the Agency to make the correction to the Blueprint, on their behalf.

	Type/Number	Number	
AVINZA (morphine sulfate)	NDA 021260	0041	6/14/2012
BUTRANS (buprenorphine)	NDA 021306	0079	6/14/2012
DOLOPHINE (methadone hydrochloride)	NDA 006134	0011	6/13/2012
Methadone oral solution	ANDA 087997	0007	6/14/2012
Methadone oral solution	ANDA 087393	0008	6/14/2012
Methadone	ANDA 089897	0005	6/13/2012
DURAGESIC (Fentanyl Transdermal System)	NDA 019813	0072	6/19/2012
EMBEDA (morphine sulfate and naltrexone hydrochloride)	NDA 022321	0064	6/14/2012
EXALGO (hydromorphone HCl)	NDA 021217	0088	6/14/2012
KADIAN (morphine sulfate)	NDA 020616	0020	6/14/2012
MS CONTIN (morphine sulfate)	NDA 019516	0023	6/14/2012
NUCYNTA ER (tapentadol)	NDA 200533	0065	6/14/2012
OPANA ER (oxymorphone hydrochloride)	NDA 201655	0046	6/14/2012
OPANA ER (oxymorphone hydrochloride)	NDA 021610	0041	6/14/2012
OXYCONTIN (oxycodone hydrochloride	NDA 020553	0068	6/14/2012
OXYCONTIN (oxycodone hydrochloride	NDA 022272	0136	6/14/2012

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

3.1 OVERVIEW OF FINAL REMS AND REMS ASSESSMENT PLAN

An overview of the final agreed upon ER/LA Opioid Analgesic REMS and REMS Assessment Plan is included below. The complete, final agreed upon REMS and the REMS Assessment Plan are attached to this review.

ER/LA Opioid Analgesic REMS

I. 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.

II. REMS Elements

A. Medication Guide

B. Elements to Assure Safe Use

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

III. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter.

REMS Assessment Plan

The REMS assessment plan includes eight components: 1) an assessment of the number of prescribers who have completed REMS-compliant training, 2) a summary of independent audits of training, 3) evaluation of healthcare provider understanding of the training information using surveys, 4) evaluation of patient understanding of the safe use of ER/LA opioids using surveys, 5) surveillance of abuse, misuse, overdose, addiction and death from ER/LA opioids, 6) evaluation of drug utilization patterns, 7) evaluation of prescribing behaviors, and 8) monitoring patterns of prescribing that suggest changes in patient access to ER/LA opioids.

3.2 RESULTS OF REVIEW

All REMS materials were developed with input from, and cleared by the Opioid REMS SSC. The rationale for the design of the REMS and REMS materials is discussed in the Executive Memorandum dated July 6, 2012. Highlights of DRISK's review, from the

original August 2011 submissions to the final submissions received in June 2012, are included below.

Of the documents included in the original, August 2011 submission, DRISK was assigned to review the REMS document, two letters (one prescriber letter and one professional organization/licensing board letter), and select sections of the REMS Supporting Document. As noted previously, DRISK provided comments on the other materials as part of the larger review team.

REMS Document

The REMS document that was originally submitted was not in a reviewable format and contained a considerable amount of extraneous information (e.g. contained extensive background information). Hence, with the exception of the REMS goals (originally communicated to the RPC in the April 2011 letter) the REMS document had to be completely re-written by the Agency to conform to current standards and expectations for the single shared system.

REMS Letters to Prescribers and Professional Organizations

The REMS letters were consistent with the requirements in the April 2011 Notification letter and contained content to inform prescribers of: the existence of the REMS, the need to complete the necessary training, and the availability of the Patient Counseling Document; the REMS letters were to be sent within 30 calendar days of the availability of the first certified continuing education training.

Several months into the review, the RPC informed the Agency that the first prescriber training would not be available for at least nine months after the approval of the REMS (due to the process of awarding educational grants and time needed for CE providers to develop the training programs). Hence, distribution of the REMS letters would also be delayed. The Agency determined that this substantial delay, both in announcing the REMS approval and the availability of the Patient Counseling Document, was unacceptable. Therefore, after further discussion, it was decided that three letters would need to be distributed at the following times: 1) within 30 days of the REMS approval, a letter informing prescribers about the existence of the REMS and the Patient Counseling Document, and the future availability of REMS-compliant training, 2) within 30 days of the availability of the first REMS-compliant training, a letter notifying prescribers of the training's availability, and 3) at least annually from the date of initial REMS approval, a letter to newly registered DEA-prescribers, informing them about the REMS. The first two letters were also to be sent to professional organizations/licensing entities. The target audiences for these letters or "entities" to receive these letters, which are listed in the REMS document, were proposed by the RPC.

REMS Website & Call-Center

The RPC referenced a REMS website in their proposed REMS document, but did not include a reviewable website prototype in their original submission. The prototype that was ultimately submitted required numerous rounds of revisions to ensure that the appropriate information was captured, was easily accessible, and presented clearly.

In working with the RPC to develop their website, the need for a single point of contact for questions about the REMS, led to a considerable amount of discussion. Instead of providing a single, toll-free number on the website, for any product-specific questions or concerns, as well as to request the ER/LA opioid REMS materials, the RPC originally proposed providing a list of the individual companies' toll-free number, as well as a list organized by product name. DRISK notified the RPC that their proposed approach was not user friendly, and therefore not acceptable. Additionally, given the significant amount of publicity expected around this REMS' approval, and in anticipation of possible confusion with the already approved TIRF REMS (see Section 4), it would be important to have a more reliable way for stakeholders to ask general questions about the REMS and to obtain REMS materials.

Therefore, DRISK requested that the RPC establish a centralized call center that could be accessed via a single, toll-free number. This centralized call center could then direct product-specific calls to the respective NDA/ANDA holders' call centers, if necessary. Initially, the RPC stated that establishing a fully operational, centralized call center would take approximately 9-10 months, which would include a period of roughly 2-3 months after the approval of the REMS. DRISK believed that this delay would be too significant and that an interim solution would need to be developed, as our experience with previous REMS has shown that call volume is highest in the months following REMS approval and implementation.

After re-evaluating their timeline for call center implementation, the RPC believed that they would be able to have an operational, centralized call center established by July 23, 2012. However, the RPC wanted to have an interim solution available as an option, in the event the centralized call center was not fully operational. DRISK requested that a proposal of the interim solution be submitted for review. After a few revisions, DRISK accepted the RPC's approach.

DRISK informed the RPC that an interim single toll-free number call center should be implemented no later than July 23, 2012, and a fully operational centralized call center should be implemented no later than 90 calendar days after the approval of the REMS. This language was incorporated into the REMS Document, the toll-free number was added to the letters, and details of the call center were outlined in the Supporting Document.

Supporting Document and Assessment Plan

DRISK was responsible for reviewing the operational content of the supporting document, while the SSC and members of the larger review team, particularly Division of Epidemiology and Office of Planning and Analysis, assisted greatly in drafting and reviewing the content of the REMS Assessment Plan.

The supporting documents received in the August 2011 submissions contained a copy of the REMS document and the RPC's proposed REMS Assessment Plan, but did not originally include any operational information. As the REMS program evolved over the course of the review, so did the need to include operational information in the document. DRISK worked closely with the RPC to help develop this content, including the addition of information about the call center and the process for distributing prescriber and professional association (both described in more detail above). Information describing the CE grant process was also added.

As previously described, the Assessment Plan includes eight components (see Section 3.1). Although, certain components are common to most REMS assessments, a number of unique components were included in the assessment plan. The SSC established the details for many of these unique components that are described in the supporting document, including: the expectation for independent audits from grantees and non-grantees, the plan for implementing the RPC grants, the use of special grants to obtain follow-up assessments of prescribers who have completed REMS-compliant training, the need to evaluate changes in prescribing behaviors, such as writing early refills, and suggestions for monitoring changes in patients access.

4 DISCUSSION AND CONCLUSION

As described previously, the rationale for the design of the REMS and REMS materials is discussed in the Executive Memorandum dated July 6, 2012.

In conclusion, the amended REMS for the ER/LA opioid products, received between June 13, 2012 and June 19, 2012, contains the agreed upon revisions to the REMS document, letters, website, and supporting document, as communicated, through the RPC, to the manufacturers of ER/LA opioid analgesic products. The REMS Supporting Document outlines the information and content that the applicants will use to assess the effectiveness of the ER/LA Opioid Analgesics REMS in achieving the goals.

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

5 RECOMMENDATIONS

The DRISK recommends approval of the single-shared ER/LA Opioid Analgesics REMS, as appended to this review.

ATTACHMENTS

REMS (including the appended materials)

Information Needed for Assessment of the REMS

Initial REMS Approval: 07/2012

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

GOAL

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

I. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.
    a. Training will be considered "REMS-compliant training" under this REMS if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), 3) it includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.

    b. The NDA/ANDA holders of ER/LA opioid analgesic products ("NDA/ANDA holders") will ensure that REMS-compliant training is made available to prescribers of ER/LA opioid analgesics and will achieve the following performance goals:
        i. Not later than March 1, 2013, the first REMS-compliant training will be made available.
        ii. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained;
        iii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained;
        iv. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60%

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

c. The content of the REMS-compliant training will be based on the learning objectives established by the FDA Blueprint. The FDA Blueprint contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics. The NDA/ANDA holders will direct providers of REMS-compliant training to the FDA Blueprint, via the REMS website (www.ER-LA-opioidREMS.com), and via its Request for Grant Applications. No less than annually, NDA/ANDA holders will direct providers of REMS-compliant training to consult the FDA Blueprint for possible revisions (e.g., changes to the drug specific information).

d. NDA/ANDA holders will ensure that independent audits of the educational materials used by the providers of REMS-compliant training are conducted. The audits must:
    i. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
    ii. Evaluate:
        1. whether the content of the training covers all components of the FDA Blueprint approved as part of the REMS;
        2. whether the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
        3. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education® (ACCME®), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession.
    iii. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals in section B.1.b.

e. To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders will make available, and then

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

i. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
ii. A copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics.
iii. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter) (see section B.1.f).

f. To make prescribers aware of the existence of the REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs:

i. Prescriber Letter 1 will be sent not later than 60 days after the initial approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the Patient Counseling Document (PCD).

ii. Prescriber Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.

iii. The prescribers will be identified via the DEA Registration Database.

iv. At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and Prescriber Letter 3 will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the Patient Counseling Document (PCD), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.

g. To further ensure that prescribers are aware of the existence of the ER/LA Opioid Analgesic REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail the following two letters to the professional organizations and state licensing entities

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

i. Professional Organization/Licensing Board Letter 1 will be sent not later than 60 days after the approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids.

ii. Professional Organization/Licensing Board Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.

iii. The letter and enclosures referenced above, will be sent to the following entities:

a) State Licensing Boards of:

1) Medicine (allopathic and osteopathic)
2) Nursing
3) Dentistry

b) Associations of State Licensing Boards:

1) Federation of State Medical Boards
2) National Council of State Boards of Nursing
3) American Association of Dental Boards

c) Learned Societies and Professional Associations, including, but not limited to:

1) American Academy of Addiction Psychiatry
2) American Academy of Family Physicians
3) American Academy of Hospice and Palliative Medicine
4) American Academy of Neurology
5) American Academy of Nurse Practitioners
6) American Academy of Nursing
7) American Academy of Orofacial Pain
8) American Academy of Pain Management
9) American Academy of Pain Medicine
10) American Academy of Physical Medicine and Rehabilitation

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

41) American College of Emergency Physicians

42) Society of Emergency Medicine Physician Assistants

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

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

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

II. Implementation System

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

III. Timetable for Submission of Assessments

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

Patient Counseling Document (PCD)

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** break, chew, crush, dissolve, 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 • 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. 2012 *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria*. Accessed on March 30, 2012.
[2]Accreditation Council for Continuing Medical Education. 2012. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support*. Accessed on March 30, 2012.

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

Why Prescriber Education is Important

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

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.[3]
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.[4]
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.[5]
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

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

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

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

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

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

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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 March 30, 2012.

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

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

ii. Abuse by patient or household contacts.
iii. Misuse and addiction.
iv. Physical dependence and tolerance.
v. Interactions with other medications and substances (See table in Section VI for specific information).
vi. Inadvertent exposure by household contacts, especially children.

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

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

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

III. Managing Therapy with ER/LA Opioid Analgesics

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

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

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

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

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

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

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

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

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

hormone (ADH).

v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.

vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See table in Section VI for specific information).

e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.

i. Patients must be opioid tolerant before using any strength of
- Transdermal fentanyl, or
- ER hydromorphone.

ii. For other ER products, patients must be opioid tolerant before using
- Certain strengths, or
- Certain daily doses.

iii. See table in Section VI for specific information.

f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.

g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

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

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

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) **Dolophine** (methadone HCl tablets) **Embeda** (morphine sulfate ER-naltrexone capsules) **Kadian** (morphine sulfate ER capsules) **Nucynta ER** (tapentadol HCl ER tablets) **OxyContin** (oxycodone HCl CR tablets)	**Butrans** (buprenorphine transdermal system) **Duragesic** (fentanyl transdermal system) **Exalgo** (hydromorphone HCl ER tablets) **MS Contin** (morphine sulfate CR tablets) **Opana ER** (oxymorphone HCl ER tablets)
Dosing Interval	▪ Refer to individual product information.
Key Instructions	▪ 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. ▪ See individual product information for the following: • Dosage reduction for hepatic or renal impairment.
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. ▪ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	▪ 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	▪ 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 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. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
Key Instructions	▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application • 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, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 10 mcg/hr and 20 mcg/hr transdermal systems are for use in opioid-tolerant patients only.
Drug-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 8 to 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	▪ Pharmacokinetic drug-drug interactions with methadone are complex. ▪ CYP 450 inducers may increase methadone levels. ▪ CYP 450 inhibitors may decrease 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 no less than 72 hour intervals. • Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. **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.
Use in Opioid-Tolerant	All doses of Duragesic are indicated for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Patients	
Product-Specific Safety Concerns	▪ 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 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. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg or 16 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 using a minimum of 3 to 4 day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfa 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 sulfa 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, 50 mg, 60 mg, 80 mg, 100 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. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg and 200 mg capsules are for use in opioid-tolerant patients.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	▪ 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 using a minimum of 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	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	▪ Oxycodone Hydrochloride ▪ Controlled-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 with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	▪ 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.
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.	

Prescriber Letter #1

FDA-Required REMS Program for Serious Drug Risks

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

Dear **DEA**-Registered Prescriber:

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

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

The principal components of this REMS are:

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

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

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

Prescriber Action

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

- **Train (Educate Yourself) -** Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for your discipline. This training is being developed and will be offered early next year at no or nominal cost to prescribers. You will be notified when REMS-compliant training will become available. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

- **Counsel Your Patients -** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. The enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) should be used to facilitate these discussions.

- **Emphasize Patient and Caregiver Understanding of the Medication Guide -** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as the information in the Medication Guide may have changed.

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

REMS-compliant Training Programs

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

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

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

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

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household members – to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

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

Adverse Event Reporting

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

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

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

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

Prescriber Letter #2

FDA-Required REMS Program for Serious Drug Risks

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

Dear **DEA**-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid 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

Prescriber Letter #3

FDA-Required REMS Program for Serious Drug Risks

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

Dear **DEA**-Registered Prescriber:

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

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

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

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

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

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

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

Prescriber Action

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

- **Train (Educate Yourself) -** Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

- **Counsel Your Patients –** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.

- **Emphasize Patient and Caregiver Understanding of the Medication Guide -** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

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

REMS-compliant Training Programs

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

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

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

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

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

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household members– to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

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

Adverse Event Reporting

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

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

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

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

Professional Organization/Licensing Board Letter #1

FDA-Required REMS Program for Serious Drug Risks

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

Dear **<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,
- 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/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

The core messages include:

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

[1] **The branded and generic drug products subject to this REMS include *all***: a) extended-release, oral-dosage forms containing: 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

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

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

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

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

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

Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program

Materials for Healthcare Professionals

ER/LA Opioid Analgesics REMS-Compliant Training

Dear DEA-Registered Prescriber Letters

Patient Counseling Document

Medication Guides

Healthcare Professional Frequently Asked Questions *(Coming Soon)*

Materials for Patients

Medication Guides

Patient Frequently Asked Questions *(Coming Soon)*

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

ER/LA Opioid Analgesics REMS

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

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

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

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

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

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

Click here for a complete list of products covered under the ER/LA Opioid Analgesics REMS Program

For Additional Information about the ER/LA Opioid REMS Program, Call 800-503-0784.

Materials for Healthcare Professionals

ER/LA Opioid Analgesics REMS-Compliant Training

Dear DEA-Registered Prescriber Letters

Patient Counseling Document

Medication Guides

Healthcare Professional Frequently Asked Questions *(Coming Soon)*

Materials for Patients

Medication Guides

Patient Frequently Asked Questions *(Coming Soon)*

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

ER/LA Opioid Analgesics REMS-Compliant Training

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

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

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

These core messages include:

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

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

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

Links

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

Listing of REMS-compliant training programs from accredited CE providers *(Coming Soon)*

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

Dear DEA-Registered Prescriber Letters

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

- Dear DEA-Registered Prescriber Letter 1 - Announcing REMS approval

Patient Counseling Document

What is the Patient Counseling Document?

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

How can I obtain copies of the PCD?

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

Materials for Download

Patient Counseling Document (PCD)

PCD Order Form

ER/LA Opioid Analgesics REMS

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

Products covered under the ER/LA Opioid Analgesics REMS Program

Brand Name Products

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

*No longer being marketed, but is still approved.
***Not currently available or marketed due to a voluntary recall, but is still approved.

Generic Products

Drug Name	Generic Name	Company	Contact	Links
Fentanyl	Fentanyl extended-release transdermal system	Actavis	1-877-422-7452	• U.S. Prescribing Information

				• Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Mallinckrodt	1-800-778-7898	• U.S. Prescribing Information • Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies, Inc.	1-877-446-3679	• U.S. Prescribing Information • Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Noven Pharmaceuticals, Inc.	1-800-667-4708	• U.S. Prescribing Information • Medication Guide
Fentanyl	Fentanyl extended-release transdermal system	Sandoz Inc.	1-800-525-8747	• U.S. Prescribing Information • Medication Guide
Fentanyl	Fentanyl transdermal system	Watson Laboratories, Inc	1-800-272-5525	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Mallinckrodt	1-800-778-7898	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Roxane Laboratories, Inc.	1-800-962-8364	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride Intensol™ oral concentrate	Roxane Laboratories, Inc.	1-800-962-8364	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride Oral Solution	Roxane Laboratories, Inc.	1-800-962-8364	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride tablets	Sandoz Inc.	1-800-525-8747	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride Tablets	ThePharmaNetwork, LLC	1-877-272-7901	• U.S. Prescribing Information • Medication Guide
Methadone Hydrochloride	Methadone hydrochloride oral solution	VistaPharm, Inc.	(727) 530-1633	• U.S. Prescribing Information • Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Vintage Pharmaceuticals, LLC, d/b/a Qualitest Pharmaceuticals	1-800-444-4011	• U.S. Prescribing Information • Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Mallinckrodt	1-800-778-7898	• U.S. Prescribing Information • Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Mylan Pharmaceuticals Inc.	1-877-446-3679	• U.S. Prescribing Information • Medication Guide
Morphine Sulfate	Morphine sulfate extended-release tablets	Rhodes Pharmaceuticals L.P.	1-888-827-0616	• U.S. Prescribing Information • Medication Guide
Morphine Sulfate	Morphine sulfate extended-release capsules	Watson Laboratories, Inc	1-800-272-5525	• U.S. Prescribing Information • Medication Guide
Oxycodone Hydrochloride	**Oxycodone hydrochloride extended-release tablets	Vintage Pharmaceuticals, LLC, d/b/a Qualitest Pharmaceuticals	1-800-444-4011	• U.S. Prescribing Information • Medication Guide
Oxycodone Hydrochloride	**Oxycodone hydrochloride extended-release tablets	Mallinckrodt	1-800-778-7898	• U.S. Prescribing Information • Medication Guide
Oxymorphone Hydrochloride	Oxymorphone hydrochloride extended-release tablets	Actavis	1-800-422-8534	• U.S. Prescribing Information

				• Medication Guide

**Tentatively approved products.

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

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

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

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

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

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

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

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

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

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

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

Adverse Event Reporting

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

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

Patient Counseling Document and Medication Guide

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

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

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

Information Needed for Assessment of the REMS

1. The first REMS assessment, due not later than six months from the date of REMS approval letter, should provide a report on the actions you have taken to implement the REMS since it was approved. The report should include the following information:

    a. Grant Proposals: The status of the requests for proposals for grants for CE training including: 1) how many have issued and when will the next requests for proposals issue; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each of the grantees will make their CE training available; 6) a high-level description of each program (e.g., web based, live); and 7) an estimate of how many prescribers are expected to be trained under each program.

    b. Evaluation Grants: The status of the requests for proposals for special grants to CE providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken training funded under this REMS to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

    c. Functional Components:

        i. Date when the ER/LA Opioid REMS website was live and functional.

        ii. Prescriber Letter 1: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

        iii. Professional Organization/Licensing Board Letter 1: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.

        iv. Date when the single number toll free call center was operational.

        v. Call Center: 1) Summary of frequently asked questions, 2) Problems reported, and 3) ER/LA Opioid Analgesics REMS questions versus product-specific questions.

2. The second REMS assessment, due one year from the date of this letter, should include the following information:

    a. Functional Components:

i. Training: 1) Date the first REMS-compliant training was available; 2) a high-level description of the training (e.g., web based, live); 3) the number of prescribers that have undergone the training, and 4) an estimate of how many prescribers will be trained under the program(s).

ii. Prescriber Letter 2: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

iii. Professional Organization/Licensing Board Letter 2: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.

iv. Call Center: 1) Summary of frequently asked questions, 2) Problems reported, and 3) ER/LA Opioid Analgesics REMS questions versus product-specific questions.

b. Grant Proposals: An update on the status of the requests for proposals for grants for REMS-compliant training, including: 1) new grant requests for proposals published; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each grantee will make or has made their REMS-compliant training available; 6) a high-level description of each program (e.g., web based, live), and 7) an estimate of how many prescribers will be trained under each program.

c. Evaluation Grants: The status of the requests for proposals for special grants to CE providers who also agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken their ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

3. The third REMS assessment, due two years from the date of this letter, should include the following information:

a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:

i. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;

ii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;

iii. Within four years from the time the first REMS- compliant training becomes available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.

c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS–compliant training for purposes of meeting the milestones in 3b., and must evaluate:

i. whether the content of the training covers all elements of the FDA "blueprint" approved as part of the REMS;

ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA "blueprint"; and

iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.

d. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients.

e. Surveillance Results: Results of surveillance for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.

f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;

g. Patient Access: An evaluation of changes in patients' access to ER/LA Opioids.

h. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

i. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

4. The fourth and subsequent REMS assessments should include the following information:

a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.

b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training (see 3b above).

c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training (see 3c above).

d. Evaluation of Prescriber Understanding:

i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.

ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.

e. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. (See 3d above).

f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 3e above).

g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 3f above).

h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.

i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

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/s/

DANIELLE SMITH
07/06/2012

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07/06/2012
concur