

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

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

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

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

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

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

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

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

¹Accreditation Council for Continuing Medical Education. 2016. *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria*. Accessed on July 20, 2016.

²Accreditation Council for Continuing Medical Education. 2016. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support*. Accessed on July 20, 2016.

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

Why Prescriber Education is Important

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

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

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products. ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

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

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

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

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

³Substance 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 July 20, 2016.

⁴Substance 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 July 20, 2016.

⁵Warner 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 July 20, 2016.

- ii. Life-threatening respiratory depression
 - iii. Abuse by patient or household contacts
 - iv. Misuse and addiction.
 - v. Physical dependence and tolerance.
 - vi. Interactions with other medications and substances (See [table in Section VI](#) for product-specific information).
 - vii. Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy.
 - viii. Inadvertent exposure/ingestion by household contacts, especially children.
- b. Prescribers should assess each patient’s risk of abuse, including substance use and psychiatric history. Prescribers should:
- i. Obtain a complete history and conduct a complete physical examination. The history should include assessment for a family history of substance abuse and psychiatric disorders, as well as special considerations regarding dose and adverse effects in geriatric patients, pregnant women, and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid-tolerant patients. (See [table in Section VI](#) for product-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. (See [table in Section VI](#) for product-specific information)
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability. (See individual product labeling)
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.

- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids and monitor patients closely, especially at the time of treatment initiation and dose increases.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
- c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
- d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
- e. Prescribers should be aware that there are no adequate and well-controlled studies of ER/LA opioid analgesics in pregnant women. ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
- f. Prescribers should be aware of the pregnancy status of their patients. If opioid use is required for a prolonged period in a pregnant woman, prescribers should advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- g. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
- h. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
- i. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

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

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.

- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients and caregivers that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed. In addition, patches and buccal films should not be cut, torn, or damaged prior to use. Manipulating the ER/LA opioid analgesic described above 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 and caregivers 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 and caregivers should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.
- h. Prescribers should instruct patients and caregivers to tell all of their doctors about all medications the patient is taking.
- i. Prescribers should warn patients and caregivers not to abruptly discontinue or reduce the ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients and caregivers that ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients or caregivers should call their prescriber for information about managing side effects.
- m. Prescribers should explain to patients and caregivers 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 and caregivers to store ER/LA opioid analgesics in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients and caregivers that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients and caregivers to dispose of any ER/LA opioid analgesics when no longer needed by flushing them down the toilet.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>.

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

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

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
 - i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
 - ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.
 - vii. See [table in Section VI](#) for product-specific information.
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of ER/LA opioid analgesics.
 - i. For ER products, patients must meet the criteria for opioid tolerance, described in the [table in Section VI](#), before using:
 - a. certain products,
 - b. certain strengths,
 - c. certain daily doses, and
 - d. in specific indicated patient populations (e.g., pediatric patients).
 - ii. See the [table in Section VI](#) for product-specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.
- h. For buccal film products, the film should not be applied if it is cut, damaged, or changed in any way. Use the entire film.
 - i. Follow the instructions for conversion in the Dosage and Administration section (2.1) in the *Prescribing Information* of each product when converting patients from one opioid to another.

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

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference.

The completed table can be found at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf>. The product specific information contained in the section titled **Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)** is maintained and updated by the Food and Drug Administration based on each individual product's approved Prescribing Information. 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)	
Dosing Interval	<ul style="list-style-type: none"> ▪ Refer to individual product information.
Key Instructions	<ul style="list-style-type: none"> ▪ Limitations of usage: <ul style="list-style-type: none"> • Reserve for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Not for use as an as-needed analgesic. • Not for mild pain or pain not expected to persist for an extended duration. • Not for use in treating acute pain. ▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. ▪ Solid oral dosage forms: <ul style="list-style-type: none"> • Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. • Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. • Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. • Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: <ul style="list-style-type: none"> • Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. • Location of application must be rotated. • Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ Buccal film dosage form: <ul style="list-style-type: none"> • Do not use if the package seal is broken or the film is cut, damaged, or changed in any way. ▪ See individual product information for the following: <ul style="list-style-type: none"> • Dosage reduction for hepatic or renal impairment.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Interactions Common to the Class	<ul style="list-style-type: none"> ▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and butorphanol) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Adult patients considered opioid-tolerant are those receiving, for one week or longer: <ul style="list-style-type: none"> ○ 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 ▪ Pediatric patients (11 years and older) considered opioid-tolerant are those who are already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (applicable to OxyContin's pediatric indication only) ▪ See individual product information for which products: <ul style="list-style-type: none"> • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.
Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) ▪ See individual product information for additional contraindications.
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Name	
Dosing Interval	
Key Instructions	
Specific Drug Interactions	
Use in Opioid-Tolerant Patients	
Product-Specific Safety Concerns	
Relative Potency to Oral Morphine	