

Opioid Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics are opioids and Schedule II or Schedule III controlled substances with abuse liabilities similar to other opioids. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression. Prescribers and patients should consult the ER/LA opioid individual Full Prescribing Information and Medication Guides for further safety information.

ER/LA opioid analgesics can be abused in a manner similar to other opioids, legal or illicit. This should be considered in situations where there are concerns about an increased risk of misuse, abuse, or diversion.

Addiction can occur in patients appropriately prescribed and in recommended doses of ER/LA opioid analgesics, and if misused or abused. Persons at increased risk for opioid abuse and addiction 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 require careful monitoring for signs of misuse, abuse and addiction.

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

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, ER/LA opioid analgesics should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics, immediate-release opioids, or non-medication therapies) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. For some 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, 60 mg oral hydrocodone per 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.

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

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

- **ER/LA Opioid Analgesics exposes users to the risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions.**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ER/LA Opioid Analgesics tablets whole to avoid exposure/ingestion to a potentially fatal dose.**
- **Accidental exposure/ingestion of ER/LA Opioid Analgesics, especially in children, can result in a fatal overdose.**
- **Prolonged use of ER/LA Opioid Analgesics during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**
- **Initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose.**
- **Concomitant use with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.**

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 gastrointestinal obstruction, including paralytic ileus. **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, hydrocodone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

If you have questions about these terms, consult your physician. For more information about active ingredients and contraindications of specific ER/LA opioids, you should consult the

product's Full Prescribing Information and Medication Guides. <http://www.er-la-opioidrems.com/lwgUI/rems/home.action>.

Adverse Reactions

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

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

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

With respect to laboratory monitoring, not every urine drug test for "opioids" or "opiates" detects opioids (particularly synthetic or semi-synthetic opioids) reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for opioids is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

Adverse Event Reporting

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

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

REMS, Patient Counseling Document and Medication Guide

The FDA has required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics. The REMS is a strategy to manage known or potential

serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. More information is available at <http://www.er-la-opioidrems.com/lwgUI/rems/home.action>.

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to the 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 the REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely. The PCD is available at <http://www.er-la-opioidrems.com/lwgUI/rems/pcd.action>.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as prescribed, 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 patients 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.