Opioid Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

Extended-Release and Long-Acting (ER/LA) and immediate-release (IR) prescription opioid analgesics are Schedule II or Schedule III controlled substances with a high potential for abuse and risk of fatal overdose due to respiratory depression. Prescribers and patients should consult the individual opioid Full Prescribing Information and Medication Guides for further safety information, available at https://opioidanalgesicrems.com/RpcUI/home.u

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 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.

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, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.**

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, opioid analgesics should be reserved for use in patients for whom alternative treatment options 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.

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 and IR opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations for patients who are opioid tolerant and those that are not opioid tolerant.

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:

- **Opioid analgesics expose 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.**
- **A Risk Evaluation and Mitigation Strategy (REMS) is required by FDA for opioid analgesics and REMS-compliant education programs are available to healthcare providers. Healthcare providers are strongly encouraged to complete a REMS-compliant education program; counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products; emphasize the importance of reading the Medication Guide every time it is provided by their pharmacist, and; consider other tools to improve patient, household, and community safety.**
- **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 opioid analgesics, especially in children, can result in a fatal overdose.**
- **Prolonged use of 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.**
- **The concomitant use of certain opioid analgesics with cytochrome P450 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.**
- **Concomitant opioid 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.**

Opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of the opioid analgesic, 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 opioid analgesic;** therefore, the Full Prescribing Information for the individual opioid analgesic must be consulted.

If you have questions about these terms, consult your physician. For more information about active ingredients and contraindications of specific opioids, consult the product's Full Prescribing Information and Medication Guides, available at https://opioidanalgesicrems.com/RpcUI/home.u.

Adverse Reactions

Serious adverse reactions of opioid analgesics include addiction, abuse, and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, interactions with

benzodiazepines and other CNS depressants, adrenal insufficiency, severe hypotension, gastrointestinal adverse reactions, seizures, and withdrawal.

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

Certain opioids, at certain doses, have been shown to prolong the QTc interval. Refer to the individual Full Prescribing Information for specific Warning information.

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

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for all opioid analgesics. The 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. More information is available at https://opioidanalgesicrems.com/RpcUI/home.u.

The Patient Counseling Guide on opioids analgesics is a tool unique to the REMS designed to facilitate important discussions with your patients for whom you select an opioid analgesic. The Patient Counseling Guide 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 the REMS and includes space for you to write additional information to help your patients use their opioid analgesic safely. The Patient Counseling Guide is available at https://opioidanalgesicrems.com/RpcUI/patientCounsellingGuide.u.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store opioid analgesics securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving opioid analgesics unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused opioid analgesics should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines..

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 opioid analgesic prescribed.