



Reference Materials and Resources



Boston University School of Medicine
Continuing Medical Education

EXTENDED-RELEASE/LONG-ACTING OPIOID ANALGESICS

Class and Drug-specific information

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) Butrans (buprenorphine transdermal system) Dolophine (methadone HCl tablets) Duragesic (fentanyl transdermal system) Embeda (morphine sulfate ER-naltrexone capsules) Exalgo (hydromorphone HCl ER tablets) Kadian (morphine sulfate ER capsules) MS Contin (morphine sulfate CR tablets) Nucynta ER (tapentadol HCl ER tablets) Opana ER (oxymorphone HCl ER tablets) OxyContin (oxycodone HCl CR 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.

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.

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. • 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: - o Have strengths or total daily doses only for use in opioid-tolerant patients. - o 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

**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 - o Apply only to sites indicated in the Full Prescribing Information. - o Apply to intact/non-irritated skin. - o Skin may be prepped by clipping hair, washing site with water only - o Rotate site of application a minimum of 3 weeks before reapplying to the same site. - o Do not cut. • Avoid exposure to heat. • Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	• CYP3A4 Inhibitors may increase buprenorphine levels. • CYP3A4 Inducers may decrease buprenorphine levels. • Benzodiazepines may increase respiratory depression. • Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 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
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.

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.

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 - o Apply to intact/non-irritated/non-irradiated skin on a flat surface. - o Skin may be prepped by clipping hair, washing site with water only - o Rotate site of application. - o Titrate using no less than 72 hour intervals. - o 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 Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	• Accidental exposure due to secondary exposure to unwashed/unclothed application site. • Increased drug exposure with increased core body temperature or fever. • Bradycardia • Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid

Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	• Initial dose as first opioid: 20 mg/0.8 mg. • Titrate using a minimum of 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

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.

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). • 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

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.

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. • 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

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.

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.

Extended Release/Long-Acting Opioids

General Drug Safety Information

This document is provided as a SUMMARY only of side effects and potential drug-drug interactions, for your reference as you prescribe ER/LA Opioids. Please consult the following for more information:

- www.er-la-opioidrems.com/lwgUl/remS/pdf/important_safety_information.pdf for general safety information
- www.er-la-opioidrems.com/lwgUl/remS/products.action for DETAILED product-specific information, including side effects and contraindications

ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.

SIDE EFFECTS:

- **MOST COMMON:** Constipation. This should be anticipated, and discussed with your patients.
- **MOST SERIOUS:** Respiratory depression (RD). Patients should be monitored for respiratory depression. You should explain the relative risks and describe appropriate measure to take (including calling 911), as RD can be immediately life-threatening.

DRUG INTERACTIONS AND COMPLICATIONS:

- **CNS depressants.** ER/LA Opioids are also CNS depressants; combining them with any of the substances below can increase the sedation and respiratory depression effected by the opioids.
 - Alcohol
 - Sedatives
 - Hypnotics
 - Tranquilizers
 - Tricyclic antidepressants
- **“Dose Dumping”.** Exposure to alcohol may cause rapid release of some ER opioid formulations. Alcohol exposure may cause some opioid drug levels to increase, even without dose dumping.
- **MAOIs.** Use of opioids with MAOIs may result in possible increase in respiratory depression. Use of certain opioids with MAOIs may cause serotonin syndrome (interference with serotonin metabolism, resulting in neuromuscular, autonomic, and behavioral changes due to increased CNS serotonin activity)
- **Diuretics.** Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- **QTc interval.** Methadone and buprenorphine can prolong the QTc interval, increasing the risk of sudden cardiac death.
- **MRIs.** Patients should NOT wear transdermal fentanyl during MRIs (because of the metal foil backing on the patch)

TOLERANCE TO SEDATING AND RESPIRATORY-DEPRESSANT EFFECTS:

- Patients **MUST** be opioid tolerant before using any strength of
 - Transdermal fentanyl
 - ER hydromorphone
- Other ER/LA opioids require patients to be opioid tolerant before using
 - Certain strengths
 - Certain daily doses
- See FDA table for details

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.

Extended Release/Long-Acting Opioids

Basic Patient Counseling Talking Points

Your patients need some basic information about the safe use of Extended Release/Long-Acting Opioids. This information provided here is an outline of those points which should be communicated clearly to patients, whether they are just starting ER/LA Opioid therapy or managing their pain long-term with chronic opioid therapy. This document can be printed and kept handy in your office for easy reference. Please also refer to the Patient Counseling Document.

1. **PRINT and distribute product-specific information; confirm that patients and/or caregivers will read it**
(available here: www.er-la-opioidrems.com/lwgUI/rems/products.action)
2. **EXPLAIN details of how to take the medication**
 - a. Specific dosage
 - b. When to take it
 - c. How many per day (or within a certain number of hours)
 - d. How to take if patient cannot swallow pills/capsules (refer to product-specific information)
 - e. Special handling requirements for patch
(patient should be aware that external heat, fever, and exertion can increase absorption, leading to overdose)
3. **EXPLAIN importance of adherence to regimen**
 - a. How to handle missed doses
 - b. Not to increase dosage or decrease interval OR abruptly stop taking opioids
 - c. When to call PCP (if pain is not controlled)
4. **WARN patients of what NOT TO DO**
 - a. Do NOT break, chew or crush oral medications
 - b. Do NOT cut or tear patches prior to use
 - c. Do NOT share opioids with others
 - d. Do NOT sell or give away opioids (against the law)
5. **WARN patients of adverse effects/consequences of opioids**
 - a. Describe common side effects (refer to specific medication information)
 - b. Remind patients to call PCP regarding side effects
 - c. Describe possibilities of severe side effects (including death)
 - d. Describe overdose risks (and risk of death from overdose)
6. **INSTRUCT patients on safe storage and disposal**
 - a. Lock boxes – safe from children, family members, visitors, pets
 - b. Disposal (refer to product-specific information)
 - i. Mix with coffee grounds and put in trash
 - ii. Flush down the toilet
 - iii. Find national, state, or local “take-back days”
(refer to: www.justice.gov/dea/index.shtml)

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
The <u>DOs</u> and <u>DON'Ts</u> of Extended-Release / Long - Acting Opioid Analgesics
<u>DO:</u> • 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.
<u>Call 911 or your local emergency service right away if:</u> • You take too much medicine • You have trouble breathing, or shortness of breath • A child has taken this medicine
<u>Talk to your healthcare provider:</u> • 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
<u>DON'T:</u> • 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.	

How to Dispose of Unused Medicines

Is your medicine cabinet filled with expired drugs or medications you no longer use? How should you dispose of them?

Most drugs can be thrown in the household trash, but consumers should take certain precautions before tossing them out, according to the Food and Drug Administration (FDA). A few drugs should be flushed down the toilet. And a growing number of community-based “take-back” programs offer another safe disposal alternative.

Guidelines for Drug Disposal

FDA worked with the White House Office of National Drug Control Policy (ONDCP) to develop the first consumer guidance for proper disposal of prescription drugs. Issued by ONDCP in February 2007 and updated in October 2009, the federal guidelines are summarized here:

- Follow any specific disposal instructions on the drug label or patient information that accompanies the medication. Do not flush prescription drugs down the toilet unless this information specifically instructs you to do so.
- Take advantage of community drug take-back programs that allow the public to bring unused drugs to a central location for proper disposal. Call your city or county government’s household trash and recycling service (see blue pages in phone book) to see if a take-back program is available in your community. The Drug Enforcement Administration, working with state and local law enforcement agencies, is sponsoring National Prescription Drug Take Back Days (www.deadiversion.usdoj.gov) throughout the United States.
- If no instructions are given on the drug label and no



Take drugs out of their original containers and mix them with an undesirable substance, such as used coffee grounds ...

take-back program is available in your area, throw the drugs in the household trash, but first:

- Take them out of their original containers and mix them with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets, and unrecognizable to people who may intentionally go through your trash.
- Put them in a sealable bag, empty can, or other container to prevent the medication from leaking or breaking out of a garbage bag.

FDA's Deputy Director of the Office of Compliance Ilisa Bernstein, Pharm.D., J.D., offers some additional tips:

- Before throwing out a medicine container, scratch out all identifying information on the prescription label to make it unreadable. This will help protect your identity and the privacy of your personal health information.
- Do not give medications to friends. Doctors prescribe drugs based on a person's specific symptoms and medical history. A drug that works for you could be dangerous for someone else.
- When in doubt about proper disposal, talk to your pharmacist.

Bernstein says the same disposal methods for prescription drugs could apply to over-the-counter drugs as well.

Why the Precautions?

Disposal instructions on the label are part of FDA's "risk mitigation" strategy, says Capt. Jim Hunter, R.Ph., M.P.H., senior program manager on FDA's Controlled Substance Staff. When a drug contains instructions to flush it down the toilet, he says, it's because FDA, working with the manufacturer, has determined this method to be the most appropriate route of disposal that presents the least risk to safety.

Drugs such as powerful narcotic pain relievers and other controlled substances carry instructions for flushing to reduce the danger of unintentional use or overdose and illegal abuse.

For example, the fentanyl patch, an adhesive patch that delivers a potent pain medicine through the skin, comes with instructions to flush used or left-over patches. Too much fentanyl can cause severe breathing problems and lead to death in babies, children, pets, and even adults, especially those who have not been prescribed the drug. "Even after a patch is used, a lot of the drug remains in the patch," says Hunter, "so you wouldn't want to throw something in the trash that contains a powerful and potentially dangerous narcotic that could harm others."

Environmental Concerns

Despite the safety reasons for flushing drugs, some people are questioning the practice because of concerns about trace levels of drug residues found in surface water, such as rivers and lakes, and in some community drinking water supplies. However, the main way drug residues enter water systems is by people taking medications and then naturally passing them through their bodies, says Raanan Bloom, Ph.D., an environmental assessment expert in FDA's Center for Drug Evaluation and Research. "Most drugs are not completely absorbed or metabolized by the body, and enter the environment after passing through waste water treatment plants."

A company that wants FDA to approve its drug must submit an application package to the agency. FDA requires, as part of the application package, an assessment of how the drug's use would affect the environment. Some drug applications are excluded from the assessment requirement, says Bloom, based on previous agency actions.

"For those drugs for which environmental assessments have been required, there has been no indication of environmental effects due to

flushing," says Bloom. In addition, according to the Environmental Protection Agency, scientists to date have found no evidence of adverse human health effects from pharmaceutical residues in the environment.

Nonetheless, FDA does not want to add drug residues into water systems unnecessarily, says Hunter. The agency reviewed its drug labels to identify products with disposal directions recommending flushing or disposal down the sink. This continuously revised listing can be found at FDA's Web page on Disposal of Unused Medicines (www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm).

Another environmental concern lies with inhalers used by people who have asthma or other breathing problems, such as chronic obstructive pulmonary disease. Traditionally, many inhalers have contained chlorofluorocarbons (CFC's), a propellant that damages the protective ozone layer. The CFC inhalers are being phased out and replaced with more environmentally friendly inhalers.

Depending on the type of product and where you live, inhalers and aerosol products may be thrown into household trash or recyclables, or may be considered hazardous waste and require special handling. Read the handling instructions on the label, as some inhalers should not be punctured or thrown into a fire or incinerator. To ensure safe disposal, contact your local trash and recycling facility.

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FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics

New boxed warning to include neonatal opioid withdrawal syndrome

The U.S. Food and Drug Administration today announced class-wide safety labeling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain.

"The FDA is invoking its authority to require safety labeling changes and postmarket studies to combat the crisis of misuse, abuse, addiction, overdose, and death from these potent drugs that have harmed too many patients and devastated too many families and communities," said FDA Commissioner Margaret A. Hamburg, M.D. "Today's action demonstrates the FDA's resolve to reduce the serious risks of long-acting and extended release opioids while still seeking to preserve appropriate access for those patients who rely on these medications to manage their pain."

Given the serious risks of using ER/LA opioids, the class-wide labeling changes, when final, will include important new language to help health care professionals tailor their prescribing decisions based on a patient's individual needs.

The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The updated indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

"The FDA's primary tool for informing prescribers about the approved uses of medications is the product labeling," said Douglas Throckmorton, M.D., deputy director for regulatory programs in the FDA's Center for Drug Evaluation and Research. "These labeling changes describe more clearly the risks and safety concerns associated with ER/LA opioids and will encourage better, more appropriate, prescribing, monitoring and patient counseling practices involving these drugs."

Recognizing that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids, the FDA is requiring the drug companies that make these products to conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death.

The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts. NOWS can occur in a newborn exposed to opioid drugs while in the mother's womb. Symptoms may include poor feeding, rapid breathing, trembling, and excessive or high-pitched crying.

In addition, the FDA is notifying ER/LA opioid analgesic application holders of the need for changes to the following sections of drug labeling: Dosage and Administration; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Patient Counseling Information, and the Medication Guide.

Once the safety labeling changes are finalized, modifications will also be made to the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), to reflect the updated information. Originally approved in 2012, the ER/LA Opioid Analgesics REMS requires companies to make available to health care

professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the safe use, storage, and disposal of ER/ LA opioids.

In addition to the safety labeling changes and postmarket study requirements, the FDA has issued responses to two related citizen petitions.

“The FDA remains committed to improving the safety of opioids and to continuing to engage in efforts to evaluate and mitigate the risks associated with opioid use,” said Dr. Throckmorton. “Today’s safety labeling changes reflect the FDA’s current understanding of the risks and benefits of these products. The FDA will evaluate the results of the postmarket studies, continue to monitor relevant safety data, and take further safety action, as warranted.”

For more information:

[New Safety Measures Announced for Extended-Release and Long-Acting Opioids](#)²

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