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. 2016. *Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria.* Accessed on February 22, 2016.
[2]Accreditation Council for Continuing Medical Education. 2016. *Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support.* Accessed on February 22, 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.

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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 February 22, 2016.

[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 February 22, 2016.

[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 February 22, 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. 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.

<table>
<tr><th colspan="2">Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)</th></tr>
<tr><td colspan="2">Avinza (morphine sulfate ER capsules)
Belbuca (buprenorphine buccal film)
Butrans (buprenorphine transdermal system)
Dolophine (methadone HCl tablets)
Duragesic (fentanyl transdermal system)
Embeda (morphine sulfate ER-naltrexone capsules)
Exalgo (hydromorphone HCl ER tablets)
Hysingla ER (hydrocodone bitartrate ER tablets)
Kadian (morphine sulfate ER capsules)
MorphaBond (morphine sulfate ER tablets)
MS Contin (morphine sulfate ER tablets)
Nucynta ER (tapentadol HCl ER tablets)
Opana ER (oxymorphone HCl ER tablets)
OxyContin (oxycodone HCl ER tablets)
Targiniq ER (oxycodone HCl/naloxone HCl ER tablets)
Troxyca ER (oxycodone HCl-naltrexone capsules)
Xtampza ER (oxycodone ER capsules)
Zohydro ER (hydrocodone bitartrate ER capsules)</td></tr>
<tr><td>Dosing Interval</td><td>▪ Refer to individual product information.</td></tr>
<tr><td>Key Instructions</td><td>▪ Limitations of usage:
• 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:
• 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.
▪ Buccal film dosage form:
• 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:
• Dosage reduction for hepatic or renal impairment.</td></tr>
</table>

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
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. ▪ 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	▪ Adult patients considered opioid-tolerant are those receiving, for one week or longer: o at least 60 mg oral morphine/day o 25 mcg transdermal fentanyl/hour o 30 mg oral oxycodone/day o 8 mg oral hydromorphone/day o 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: • 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 in increments of not greater than 30 mg using a minimum of 3 to 4 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. ▪ P-gp 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
Belbuca	Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg
Dosing Interval	Every 12 hours (or once every 24 hours for initiation in opioid naïve patients and patients taking less than 30 mg oral morphine sulfate equivalents)
Key Instructions	▪ Opioid-naïve patients or patients taking less than 30 mg oral morphine sulfate equivalents: Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 hours. • Titrate to 150 mcg every 12 hours no earlier than 4 days after initiation. • Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. ▪ When converting from another opioid, first taper the current opioid to no more than 30 mg oral morphine sulfate equivalents per day prior to initiating Belbuca. • If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate equivalents, initiate with 150 mcg dose every 12 hours. • If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate equivalents, initiate with 300 mcg dose every 12 hours. • Titration of the dose should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. ▪ Maximum dose: 900 mcg every 12 hours due to the potential for QTc prolongation ▪ Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function. ▪ Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis ▪ Do not use if the package seal is broken or the film is cut, damaged, or changed in any way

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
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 pointes.
Use in Opioid-Tolerant Patients	Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca.
Product-Specific Safety Concerns	▪ QTc prolongation and torsade de pointes ▪ Hepatotoxicity
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 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 in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20 mcg/hour ▪ 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 antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 7.5 mcg/hr, 10 mcg/hr, 15 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.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
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. ▪ Titrate slowly, with dose increases no more frequent than every 3 to 5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days). ▪ 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 decrease methadone levels. ▪ CYP 450 inhibitors may increase 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, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (**These strengths are available only in generic form*)
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 a minimum of 72 hour intervals between dose adjustments. • 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 Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure. ▪ Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.
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 1 to 2 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. ▪ P-gp 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, 16 mg or 32 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 in increments of 4 to 8 mg using a minimum of 3 to 4 day intervals ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite 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 sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Hysingla ER	Hydrocodone bitartrate Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg
Dosing Interval	Every 24 hours (once-daily)
Key Instructions	▪ Opioid-naïve patients: initiate treatment with 20 mg orally once daily. During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction. ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure ▪ Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. ▪ The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.
Use in Opioid-Tolerant Patients	A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.
Product-Specific Safety Concerns	▪ Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction. ▪ Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER. ▪ In nursing mothers, discontinue nursing or discontinue drug. ▪ QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 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 Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-patients only
Product-Specific Safety Concerns	None
MorphaBond	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 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 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MorphaBond 100 mg tablets are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Extended-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 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp 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.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
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 in increments of 5 to 10 mg using a minimum of 3 to 7-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	▪ Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	Oxycodone Hydrochloride Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ For Adults: • Initial dose in opioid-naïve and opioid non-tolerant patients is 10 mg every 12 hours. • If needed, adult dosage may be adjusted in 1 to 2 day intervals. • When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose. ▪ For Pediatric patients (**11 years and older)**: Use only in <u>opioid-tolerant</u> patients (see below, *Use in Opioid-Tolerant Patients* for dosing information). ▪ For all patients: • 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.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Use in Opioid-Tolerant Patients	▪ For Adults: • Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable potency has been established. ▪ For Pediatric patients (**11 years and older)**: • For use only in opioid-tolerant pediatric patients already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OxyContin. • If needed, pediatric dosage may be adjusted in 1 to 2 day intervals. • When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% of the current total daily dose.
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.
Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12) of Targiniq ER ▪ May be taken with or without food. ▪ Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. ▪ Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild 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.
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/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only
Product-Specific Safety Concerns	▪ Contraindicated in patients with moderate to severe hepatic impairment.
Relative Potency To Oral Morphine	▪ See individual product information for conversion recommendations from prior opioid.
Troxyca ER	Oxycodone Hydrochloride/Naltrexone Hydrochloride Extended-Release Capsules, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Opioid-naïve and opioid non-tolerant patients: 10 mg/1.2 mg, every 12 hours ▪ Total daily dose may be adjusted by 20 mg/2.4 mg every 2 to 3 days as needed ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ Crushing, chewing, or dissolving will release oxycodone, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ For patients that have difficulty swallowing, Troxyca ER, can also be taken by sprinkling the capsule contents (pellets) on applesauce and swallowing

	immediately without chewing. ▪ Do not administer Troxyca ER pellets through a nasogastric or gastric tube
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	Single doses of greater than 40 mg/4.8 mg, or a total daily dose greater than 80 mg/9.6 mg are only for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	▪ See individual product information for conversion recommendations from prior opioid.
Xtampza ER	Oxycodone Extended-Release Capsules, 9 mg 13.5 mg, 18 mg, 27 mg, and 36 mg (strengths equivalent to 10 mg, 15 mg , 20 mg, 30 mg, and 40 mg oxycodone hydrochloride, respectively)
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Opioid naïve and opioid non-tolerant patients: Initiate with 9 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Take Xtampza ER capsules with the same amount of food in order to ensure consistent plasma levels are achieved. ▪ Maximum daily dose: 288 mg (8 x 36 mg capsules) because the safety of excipients has not been established for higher doses ▪ For patients that have difficulty swallowing, Xtampza ER can also be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth and swallowing immediately. Xtampza ER may also be administered through a gastrostomy or nasogastric feeding tube. ▪ Hepatic impairment: Initiate therapy at 1/3 to 1/2 the usual dosage ▪ Renal impairment: (creatinine clearance <60 mL/min): Follow a conservative approach to dose initiation and adjust according to the clinical situation.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure ▪ CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid-Tolerant Patients	▪ A single dose greater than 36 mg or a total daily dose greater than 72 mg is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ None
Relative Potency To Oral Morphine	▪ There are no established conversion ratios for conversion from other opioids to Xtampza ER defined by clinical trials.
Zohydro ER	Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patient is 10 mg. ▪ Titrate in increments of 10 mg using a minimum of 3 to 7day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve).
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone 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.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone 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.	