SAFE Opioid Prescribing

SPEAKERS
Charles E. Argoff, MD, FABPM
Oscar A. de Leon-Casasola, MD
Bruce D. Nicholson, MD

SAFE Opioid Prescribing Strategies.
Assessment. Fundamentals. Education

Extended-Release and Long-Acting (ER/LA) Opioid Analgesics
Risk Evaluation and Mitigation Strategy (REMS)

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Program Overview

Today, clinicians are faced with the challenge of adequately treating a large number of patients with acute and chronic pain, while mitigating the risks associated with treatment. Our ability to manage pain, now competes against the crisis of opioid abuse and adverse outcomes such as addiction, unintentional overdose, and death, resulting from inappropriate prescribing, abuse, and misuse of opioids.

These complexities require clinicians to have a strong understanding of all options for pain management including non-pharmacologic and non-opioid options, as well as when to appropriately consider opioid agents when other non-opioid approaches have proven unsuccessful in alleviating pain and the benefits outweigh the risks.

This symposium is designed to fulfill specific requirements put forth by the FDA Education Blueprint for HCPs involved in the Treatment and Monitoring of Patients with Pain. Six evidence-based CME modules will address topics such as: the fundamentals of pain management, assessment of patients in pain, identifying and mitigating risk factors for abuse and addiction, and how to appropriately integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient.

Additional topics to be covered include, tools to manage patients on opioids analgesics in pain settings, including initiating therapy, titrating and discontinuing use, as well as strategies to counsel patients on safe use, disposal, and ways to identify and manage opioid use disorder or addiction.
Educational Grant in Support of this CME Activity

This educational activity is supported by an independent educational grant from the Extended-Release/Long-Acting Opioid Analgesic REMS Program Companies. Please see http://ce-er-la-opioidrems.com/lwgCEUI/remsf.pdf/List_of_RPC_Companies.pdf for a listing of REMS Program Companies. This activity is intended to be fully compliant with the Extended-Release/Long-Acting Opioid Analgesics REMS education requirements issued by the US Food & Drug Administration.

Overall Program Learning Objectives

Upon completion of this activity, the participants will be better able to:

- Implement patient assessment strategies, including tools to assess risk of abuse, misuse, or addiction when prescribing extended-release and long-acting (ER/LA) opioids
- Employ approaches to mitigate risks when initiating therapy, modifying dose, and discontinuing ER/LA opioids
- Monitor patients by evaluating treatment goals and implementing periodic urine drug testing (UDT)
- Employ patient education strategies to reduce the risks associated with the use of ER/LA opioids
- Identify similarities and differences among ER/LA opioids

Background: The Prevalence of Chronic Pain in the United States Is High

- Approximately 100 million US adults experience chronic pain (33%)
- 25.3 million US adults report daily (chronic) pain; 23.4 million report a lot of pain
- Numerous studies indicate undertreated pain: e.g., cancer, older adults, children, minorities
- Low back pain, neck pain, and osteoarthritis are among the 9 leading causes of disability
- Low back pain is the leading cause of years lived with disability in the United States and accounts for one-third of all work loss

Background: Non-Opioid Analgesic Options Are Limited

- Acetaminophen – minimal efficacy in LBP, small efficacy in OA; hepatotoxicity may occur at doses >4000 mg/d
- NSAIDs – small efficacy in LBP; FDA warning of risk for heart attack and stroke as early as the first weeks of use; GI toxicity
- Gabapentinoids and SNRIs – indicated for neuropathic pain. Efficacy for LBP and other musculoskeletal disorders uncertain
- Tricyclic antidepressants and muscle relaxants – relatively weak evidence base for chronic pain

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Background: Opioids for Chronic Pain

- Opioids may be a viable option for pain refractory to other treatments
- Recent guidelines (CDC) recognize that judicious prescribing and monitoring is appropriate for selected patients
- Placebo-controlled trials demonstrate modest efficacy
- Paucity of evidence for long-term effectiveness—true for all analgesics, not just opioids
- Goal: define most appropriate analgesic regimen for each person in pain, which may include the use of opioids (IR and ER/LA)

Kroenke K, Cheville A. JAMA. 2017;317(23):2365-2366

Ensure availability of opioids for patients with pain AND Establish systems of control to prevent abuse

Background: Opioid Abuse and Overdoses

- In 2016:
  - 91.8 million US adults used prescription opioids
  - 11.8 million misused prescription opioids
  - 2.1 million with opioid use disorder (OUD)
- The most commonly reported motivation for misuse was to relieve physical pain (63.3%)
- Misuse and use disorders most common in uninsured, unemployed, low income, behavioral health problems
- In 2015:
  - 33,091 persons died from drug overdoses involving opioids (Rx and illegal)
  - 15,281 persons died from drug overdoses involving Rx opioids
  - >30% of drug overdose deaths also included benzodiazepines


Improper use of any opioid can result in serious side effects, including overdose and death. This risk can be greater with ER/LA opioids.

Statistically Significant Changes in Drug Overdose Death Rates Involving Natural and Semi-synthetic Opioids by Select States, United States, 2014–2015

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Classifying Pain

- **Acute Pain** results from disease, inflammation, or injury to tissues
  - Comes on suddenly, e.g., post-surgery or trauma
  - The pain is self-limiting—confined to a given period of time and severity
  - Acute pain can become chronic

- **Chronic Pain** is considered a chronic disease condition
  - Can be made worse by environmental and psychological factors
  - Persists over time and is resistant to many medical treatments
  - Those with chronic pain may suffer from more than 1 painful condition
  - Common mechanisms may put some at higher risk to develop multiple pain disorders


Classifying Pain

- **Nociceptive Pain** may be thermal, chemical, or mechanical
  - In response to noxious stimuli, a message is transmitted via the primary afferent nociceptor axon from the periphery to the central nervous system (CNS)

- **Neuropathic Pain** results from injury to nerves in the peripheral or central nervous systems
  - It can occur in any part of the body and may result from diseases that affect the nerves, such as diabetes; from trauma; or as the consequence of chemotherapy for cancer
  - Often described as a hot, burning sensation
  - Neuropathic pain syndromes include diabetic neuropathy, complex regional pain syndrome, phantom limb, postherpetic neuralgia, and central pain syndrome

Goals of Risk Evaluation and Mitigation Strategy (REMS) CME on ER/LA Opioid Analgesics

- In 2012, the FDA directed all ER/LA opioid companies to provide independent CME grants to educate prescribers and to provide information for patients to:
  - Ensure that the benefits of ER/LA opioids outweigh the risks
  - Help to reduce risk for ER/LA opioid analgesics misuse, abuse, and overdose while ensuring access to pain medication
  - Follow FDA “Blueprint” on ER/LA opioids CME to engage and educate prescribers and be in compliance with standards for continuing education for physicians and other health care professionals, including Accreditation Council for Continuing Medical Education (ACCME)


Goals of This REMS-Compliant Education for ER/LA Opioid Analgesics

- As clinicians, WE are best positioned to balance treatment of pain against risks of serious adverse outcomes, including addiction, unintentional overdose, and death
- In this 6-module curriculum, we will review many best-practice aspects of managing ER/LA opioid analgesic therapy
  - Patient assessment
  - Therapy initiation, dose modification, and discontinuation
  - Therapy management
  - Counseling of patients and caregivers
  - General drug information
  - Product-specific drug information

This 6-Module Activity Is FDA REMS-Compliant CME

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Module I

Evaluation is Essential for Safe and Effective Pain Management Using ER/LA Opioids

Opioid Therapy in Chronic Pain Management

- Opioids ARE commonly prescribed for chronic pain
  - Efficacious for many types of pain, though not necessarily for all people who experience pain
  - Appropriate use is KEY to safety and success
- Goals of chronic opioid therapy:
  - Improve and/or stabilize pain intensity
  - Improve function
  - Improve quality of life (QOL)
- However, significant gaps exist between guideline recommendations for safe prescribing practices of ER/LA opioids and how they are being used in practice
  - Highlights need for further education

Opioid Therapy – Good Pain Management Principles

- Evidence-based
- Multidimensional
- Based on appropriate assessment
- A dynamic process
- But there are also risks to consider...

Risks Associated With ER/LA Opioids

- Overdose
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse and addiction
- Physical dependence and tolerance
- Interactions with other medications and substances
- Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy
- Inadvertent exposure by household contacts, especially children


Tolerance, Dependence, and Addiction—Critical Differences

What a patient who has developed tolerance to the analgesic effect of the prescribed opioid would say to you:
“‘The fentanyl patch that you prescribed used to work really well, and now it doesn’t seem to be easing as much of the pain as before. I am worried.’”

What a patient who has become physically dependent will typically say to you:
“I went up to the lake this weekend and forgot to take along my long-acting morphine. I was without it for 2 days. I got so sick that I went to the ER.”

Behavior that the addicted patient may display:
“My husband used his entire month’s supply of that extended-release opioid you gave him in 1 week. He seems like a totally different person. I am very concerned.”

Key Concepts

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance</td>
<td>State of adaptation. Exposure to a drug induces changes that result in a diminution of 1 or more of the drug’s effects over time. Indicated by a need for increasing doses to achieve the same effect. Occurs with opioids. Tolerance is not indicative of addiction.</td>
</tr>
<tr>
<td>Physical Dependence</td>
<td>State of adaptation manifested by drug class-specific withdrawal syndrome that can occur with abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence occurs in all patients using opioids for a period of time. Physical dependence is not indicative of addiction.</td>
</tr>
<tr>
<td>Addiction</td>
<td>A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental components. Characteristic behaviors include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, craving.</td>
</tr>
</tbody>
</table>

Term Definition

Abuse
Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose, such as altering one’s state of consciousness—for example, getting high.

Misuse
Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.

Aberrant Drug-Related Behavior
A behavior outside the boundaries of the agreed-on treatment plan.

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Who Misuses/Abuses Opioids and Why?

Nonmedical Use
- Recreational abusers
- Patients with disease of addiction

Medical Use
- Pain patients seeking more pain relief
- Pain patients escaping emotional pain

Examples of Misuse and Abuse

What patients will typically say to you:

“Sometimes in the morning I need to take extra pills just to get going...”

“My friend was visiting this weekend and had terrible back pain. I gave her one of my oxycodone pills. It really helped her. That’s OK, right?”

“That hydrocodone you gave my wife—well, it seems to make her feel a little too good sometimes. I think she’s taking more than you’ve prescribed and I’m worried about it...”

Prescribers Can Play an Active Role in Reducing the Risks Associated With Opioids

- Establish diagnosis
  - History and physical
  - Relevant diagnostic tests
- When opioids are being considered as part of acute or chronic pain treatment plan, complete an appropriate risk assessment
  - This is an active and ongoing process

Risk Factors for Opioid-Related Aberrant Behaviors

- Family and/or personal history of substance abuse
  - Alcohol, illegal drugs, prescription drugs
  - Prescription drug abuse history carries greater risk
- Age 16 to 45 years
- History of preadolescent sexual abuse
  - Increases risk for women
- Psychological disease
  - Attention deficit disorder (ADD) or depression
  - ADD carries higher risk
- A history of substance abuse does not preclude treatment with ER/LA

Use of Risk Stratification Tools and Ongoing Monitoring KEY to Safe and Effective Opioid Use

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Case—Peter

- 45-year-old white male, railroad worker for line maintenance and reconstruction
- S/p lumbar fusion with chronic back and leg pain
- Hx of back pain prior to injury that led to surgery, otherwise healthy
- Still experiencing pain despite multiple treatments described below

History
- Injured at work; pain on lower right side, radiating down right leg to outside of foot
  - Pain described as aching and throbbing
  - Pain severity 6/10 at rest and 7-9/10 when bending, coughing, or straining with a bowel movement
- NSAIDs, muscle relaxant, and light work duty attempted
- Patient struggled on job; complaints of severe pain

Next Steps: Make No Assumptions

- Even though the prescriber of the CR oxycodone and hydrocodone/acetaminophen has evaluated Peter’s risk for opioid misuse before initiating these drugs, should you re-assess his level of risk now that the patient is back in your care?

Yes, because the risk level can change and you want to document that you have performed a risk assessment

Peter

History (cont)
- Physical therapy (PT), X-ray, MRI (L5-S1 disc w impingement of S1 nerve root)
- Failed steroid taper, hydrocodone, epidural steroid, more PT
- Sleep deprived, anxious, withdrawn, financially stressed
- Surgery and rehabilitation – no improvement
- Pain specialist prescribed:
  - Oxycodone CR tablets 40 mg every 12 hours
  - Gabapentin 300 mg/2 tablets TID
  - Zolpidem 10 mg/HS
- Returns to your office for ongoing pain management

Peter’s Score on ORT

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
<th>Score if Female</th>
<th>Score if Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Substance Abuse</td>
<td>Alcohol</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Prescription Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Personal History of Substance Abuse</td>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Illegal Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Prescription Drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>Age 16-45 years</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>History of Preadolescent Sexual Abuse</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Psychological Disease</td>
<td>ADD, OCD, Bipolar Disorder, Schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Total Risk Score: 4

Total Score Risk Category
- Low Risk 0-3
- Moderate Risk 4-7
- High Risk ≥8

Peter – Next Steps: Make No Assumptions

- Complete history and physical – establish diagnosis
- Ask Peter about his goals for treatment:
  - Explain that complete pain relief is rarely achieved
  - Focus on functional goals, eg, return to work, work part-time, able to play golf on weekends, able to walk the dog daily
- Risk for aberrant drug behavior – Moderate (4 on ORT)
- Evaluate mental health status
- Peter’s Rx: oxycodone CR, hydrocodone/APAP, gabapentin, zolpidem – any other Rx? OTC? Drug-drug interactions?
- Re-establish care with new treatment agreement and UDT
- Peter’s household – What is the possibility of inadvertent exposure to the opioids you are prescribing by household contacts, especially children? Have you discussed safe storage?

Opioid Therapy – Ongoing Monitoring

The 4 A’s

- Assessment and Action (treatment plan)

Additional Tools for Ongoing Monitoring

Pain Assessment and Documentation Tool (PADT) – Sample Questions
Is the patient's functioning with the current pain reliever(s) better, the same, or worse since last assessment?
Is patient experiencing any side effects from current pain reliever(s)?
Check-list of potential aberrant drug-related behavior
Available at www.ucdenver.edu

Current Opioid Misuse Measure (COMM) – Sample Questions
In the past 30 days, how often have you taken your medications differently than how they are prescribed?
In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc)?
In the past 30 days, how often have you had to visit the emergency room?
Available at www.painEDU.org

Module VI

Getting the Greatest Clinical Insights from Specific ER/LA Product Information Sources

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Learning Objectives

Upon completion of this module, the participants will be better able to:

- Differentiate the prescribing information among available ER/LA opioids
- Identify ER/LA opioids and dosages indicated for opioid-tolerant patients only

Prescribers Must Be Knowledgeable

- Before prescribing an opioid, each clinician needs to be knowledgeable about specific characteristics of each available ER/LA opioid, including:
  - Drug substance
  - Formulation
  - Strength
  - Dosing interval
  - Key instructions – reserve for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain

Prescribing Information

- For detailed information, prescribers can refer to the prescribing information available online:
  - drugs@fda
  - https://www.accessdata.fda.gov/scripts/cder/daf/

Arymo ER—Morphine Sulfate

<table>
<thead>
<tr>
<th>Arymo</th>
<th>Morphine Sulfate ER Tablets, 15 mg, 30 mg, 60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Interval</td>
<td>Every 8 to 12 hours</td>
</tr>
<tr>
<td>Key Instructions</td>
<td>Initial dose in opioid-naïve and non-tolerant patients: 15 mg every 8 to 12 hours</td>
</tr>
<tr>
<td></td>
<td>Dose adjustment may be done every 1 to 2 days</td>
</tr>
<tr>
<td></td>
<td>Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth</td>
</tr>
<tr>
<td>Specific Drug Interactions</td>
<td>PGP inhibitors (eg, quinidine) can increase exposure of morphine by 2x and increase risk of respiratory depressions</td>
</tr>
<tr>
<td>Use in Opioid-Tolerant Patients</td>
<td>A single dose of arymo ER &gt; 60 mg or total daily dose &gt; 120 mg is for use in opioid-tolerant patients ONLY</td>
</tr>
<tr>
<td>Product-Specific Safety Concerns</td>
<td>Do not attempt to chew, crush, or dissolve. Swallow whole.</td>
</tr>
<tr>
<td></td>
<td>Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction</td>
</tr>
<tr>
<td>Abuse Deterrence</td>
<td>This product is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse</td>
</tr>
</tbody>
</table>

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Avinza—Morphine Sulfate ER

<table>
<thead>
<tr>
<th>Avinza</th>
<th>Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Interval</td>
<td>Once a day</td>
</tr>
<tr>
<td>Key Instructions</td>
<td>• Initial dose in opioid non-tolerant patients: 30 mg</td>
</tr>
<tr>
<td></td>
<td>• Titrate in increments of not greater than 30 mg using a minimum of 3- to-4-day intervals</td>
</tr>
<tr>
<td></td>
<td>• Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid</td>
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<tr>
<td></td>
<td>Instruct patient:</td>
</tr>
<tr>
<td></td>
<td>- Swallow capsule whole (do not chew, crush, or dissolve)</td>
</tr>
<tr>
<td></td>
<td>- May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately</td>
</tr>
<tr>
<td>Specific Drug Interactions</td>
<td>• Avoid alcoholic beverages or medications containing alcohol; may result in rapid release and absorption of potentially fatal dose of morphine</td>
</tr>
<tr>
<td></td>
<td>• PGP inhibitors (eg, quinidine) may increase absorption/exposure of morphine sulfate by approximately 2x</td>
</tr>
<tr>
<td>Use in Opioid-Tolerant Patients</td>
<td>Use 90 mg and 120 mg capsules in opioid-tolerant patients ONLY</td>
</tr>
</tbody>
</table>

Belbuca—Buprenorphine Buccal Film

<table>
<thead>
<tr>
<th>Belbuca</th>
<th>Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Interval</td>
<td>Every 12 hours (or once every 24 hours for initiation in opioid-naïve pts and those taking &lt;30 mg oral morphine equivalents)</td>
</tr>
<tr>
<td>Key Instructions</td>
<td>• Initiate treatment with a 75 mcg buccal film in opioid-naïve or if prior total daily dose of opioid &lt;30 mg oral morphine equivalents</td>
</tr>
<tr>
<td></td>
<td>• Titrate in increments of 150 mcg q 12 h</td>
</tr>
<tr>
<td></td>
<td>• The minimum titration interval is 4 days</td>
</tr>
<tr>
<td></td>
<td>• In severe hepatic impairment and in oral mucostrict, reduce dose by 50%</td>
</tr>
<tr>
<td></td>
<td>• Do not use if package seal is broken or film damaged in any way</td>
</tr>
<tr>
<td>Specific Drug Interactions</td>
<td>• CYP3A4 inhibitors may increase buprenorphine levels</td>
</tr>
<tr>
<td></td>
<td>• CYP3A4 inducers may decrease buprenorphine levels</td>
</tr>
<tr>
<td></td>
<td>• Benzodiazepines may increase respiratory depression</td>
</tr>
<tr>
<td></td>
<td>• Class IA and III antiarrhythmics and other potentially arrhythmogenic agents may increase risk for QTC prolongation and torsade de pointes</td>
</tr>
<tr>
<td>Use in Opioid-Tolerant Patients</td>
<td>600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses</td>
</tr>
<tr>
<td>Product-Specific Safety Concerns</td>
<td>• QTc prolongation and torsade de pointes</td>
</tr>
<tr>
<td>Relative Potency to Oral Morphine</td>
<td>• Equipotency to oral morphine has not been established</td>
</tr>
</tbody>
</table>

Butrans—Buprenorphine

<table>
<thead>
<tr>
<th>Butrans</th>
<th>Buprenorphine Transdermal System, 5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h, and 20 mcg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing Interval</td>
<td>One transdermal system every 7 days</td>
</tr>
<tr>
<td>Key Instructions</td>
<td>• When used as first opioid analgesic, initiate treatment with 5 mcg/h</td>
</tr>
<tr>
<td></td>
<td>• If prior total daily dose of opioid = &lt;10 mg oral morphine equivalents per day, initiate treatment with 5 mcg/h dose</td>
</tr>
<tr>
<td></td>
<td>• If prior total daily dose of opioid = 10 mg-80 mg oral morphine equivalents, taper patient’s opioid for up to 7-10 days to no more than 30 mg of morphine equivalents, then initiate with 10 mcg/h/dose</td>
</tr>
<tr>
<td></td>
<td>• The minimum titration interval is 72 hours</td>
</tr>
<tr>
<td>Instruct patient</td>
<td>• Apply only to sites indicated in full prescribing information</td>
</tr>
<tr>
<td></td>
<td>• Apply to intact/non-irritated skin</td>
</tr>
<tr>
<td></td>
<td>• Skin may be prepared by clipping hair, washing site with water only</td>
</tr>
<tr>
<td></td>
<td>• Retain site of application; allow a minimum of 5 weeks before reapply to same site</td>
</tr>
<tr>
<td></td>
<td>• Do not cut</td>
</tr>
<tr>
<td></td>
<td>• Avoid exposure to heat</td>
</tr>
<tr>
<td></td>
<td>• Dispose of used/unused patches by folding the adhesive side together and flushing down toilet</td>
</tr>
</tbody>
</table>

Drug-Specific Safety Concerns | • QTc prolongation and torsade de pointe |
|                            | • Hypersensitivity |
|                            | • Application site skin reactions |

Torsades de pointe (TdP)—a form of polymorphic ventricular tachycardia that may result in syncope or cardiac arrest.

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### Embeda—Morphine Sulfate ER-Naltrexone

#### Dosing Interval
- Once a day or every 12 hours

#### Key Instructions
- Swallow capsules whole (do not chew, crush, or dissolve)
- Instruct patient:
  - Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms.
  - If unable to swallow capsule whole, can open capsule and sprinkle pellets on applesauce; 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.
- GP inhibitors (e.g., quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold.

#### Use in Opioid-Tolerant Patients
- Use 100 mg/4 mg capsule in opioid-tolerant patients ONLY.

#### Abuse Deterrence
- This product is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

### Exalgo—Hydromorphone Hydrochloride

#### Dosing Interval
- Once a day

#### Key Instructions
- Use conversion ratios in the full prescribing information.
- Start patients with moderate hepatic impairment on 25% of the 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.
- Do not use in patients with sulfa allergy.
- Instruct patient to swallow tablets whole—DO NOT chew, crush, or dissolve.

#### Specific Drug Interactions
- None.

#### Use in Opioid-Tolerant Patients
- Use in 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 full prescribing information.

### Hysingla ER—Hydrocodone Bitartrate

#### Dosing Interval
- Once a day (every 24 hours)

#### Key Instructions
- In patients who are not opioid-tolerant, initiate therapy with 20 mg.
- Use with caution in patients with difficulty swallowing or with underlying GI disorders that may predispose them 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 CHF, bradyarrhythmias, electrolyte abnormalities, or if taking medications known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

#### Specific Drug Interactions
- CYP2D6 inhibitors may increase hydrocodone exposure.
- CYP3A4 inducers may decrease hydrocodone exposure.
- Concomitant use with strong laxatives may decrease hydrocodone absorption.
- Concomitant use of MAOIs or TCAs may increase the effect of either drug.

#### Product-Specific Safety Concerns
- Use with caution in patients with difficulty swallowing or with underlying GI disorders that may predispose them 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 CHF, bradyarrhythmias, electrolyte abnormalities, or if taking medications known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

#### Abuse Deterrence
- This product is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

### Hysingla ER—Hydrocodone Bitartrate (cont’d)

#### Dosing Interval
- Once a day

#### Key Instructions
- Use conversion ratios in the full prescribing information.
- Start patients with moderate hepatic impairment on 25% of the 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.
- Do not use in patients with sulfa allergy.
- Instruct patient to swallow tablets whole—DO NOT chew, crush, or dissolve.

#### Specific Drug Interactions
- None.

#### Relative Potency to Oral Morphine
- See individual product information for conversion recommendations from prior opioid.

#### CHF, congestive heart failure.
Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.
Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.
Targiniq ER—Oxycodone HCl/Naloxone HCl

**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
- Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In mild hepatic impairment, start with one-third to one-half usual dosage
- Renal impairment (creatinine clearance <60 mL/min): start with one-half usual dosage
- Instruct patient:
  - 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
  - Take 1 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

Targiniq ER—Oxycodone HCl/Naloxone HCl (cont’d)

**Targiniq ER**

**Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg**

**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 moderate and severe hepatic impairment
- See individual product information for conversion recommendations from prior opioid

**Relative Potency to Oral Morphine**
- See product information for conversion recommendations from prior opioid

**Abuse Deterrence**
- Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration

www.fda.gov

Troxyca ER—Oxycodone HCl/Naltrexone HCl

**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 patients: initiate treatment with 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
- Instruct patient:
  - Swallow capsule whole
  - Do NOT chew, crush, split or dissolve as this will release oxycodone, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms
  - For patients who have difficulty swallowing, Troxyca ER can be taken by sprinkling the pellets on applesauce and swallowing immediately without chewing
  - Do not administer Troxyca 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 >40 mg/4.8 mg, or a total daily dose >80 mg/9.6 mg, are for use in opioid tolerant patients ONLY

**Abuse Deterrence**
- Troxyca ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration

www.fda.gov

Vantrela ER—Hydrocodone Bitartrate

**Vantrela ER**

**Hydrocodone Bitartrate Extended-Release Tablets 15 mg, 30 mg, 45 mg, 60 mg and 90 mg**

**Dosing Interval**
Every 12 hours

**Key Instructions**
- Opioid-naïve patients: initiate treatment with 15 mg every 12 hours
- Titrate using 3- to 7-day intervals
- Renal impairment: start with half of recommended dose
- Hepatic impairment: start with half of recommended dose
- Instruct patient:
  - Swallow capsules whole
  - Do NOT chew, crush, or dissolve

**Specific Drug Interactions**
- CYP3A4 inhibitors may increase hydrocodone exposure
- CYP3A4 inducers may decrease hydrocodone exposure

**Use in Opioid-Tolerant Patients**
- Vantrela 90 mg tablets, single dose greater than 60 mg, or total daily dose greater than 120 mg are for use in opioid tolerant patients ONLY

**Abuse Deterrence**
- VANTRELA ER is formulated with pharmacologic properties intended to make the tablet
  - more difficult to manipulate for misuse and abuse.

www.fda.gov

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<table>
<thead>
<tr>
<th>XTAMPZA ER—Oxycodeone</th>
<th>ZOHYDRO ER—Hydrocodone Bitartrate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Interval</strong></td>
<td>Every 12 hours</td>
</tr>
<tr>
<td><strong>Key Instructions</strong></td>
<td></td>
</tr>
<tr>
<td>Opioid-naïve patients: initiate treatment with 9 mg every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Titrate using a minimum of 1- to 2-day intervals</td>
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<tr>
<td>Hepatic impairment: start with one-third to one-half usual dosage</td>
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<tr>
<td>Renal impairment (creatinine clearance &lt;60 mL/min): follow a conservative approach and adjust according to clinical situation</td>
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<tr>
<td>Maximum daily dose: 288 mg</td>
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<tr>
<td>For patients who have difficulty swallowing, XTAMPZA ER can be opened and sprinkled on soft foods or into a cup and immediately swallowed</td>
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</tr>
<tr>
<td>XTAMPZA ER can be administered through a feeding tube</td>
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<tr>
<td>Patient instructions: take with the same amount of food to ensure consistent plasma level are achieved</td>
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</tr>
<tr>
<td><strong>Specific Drug Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>CYP3A4 inhibitors may increase oxycodone exposure</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 inducers may decrease oxycodone exposure</td>
<td></td>
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<tr>
<td><strong>Use in Opioid-Tolerant Patients</strong></td>
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</tr>
<tr>
<td>A single dose &gt;36 mg or total daily dose &gt;72 mg</td>
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<tr>
<td><strong>Relative Potency to Oral Morphine</strong></td>
<td></td>
</tr>
<tr>
<td>There are no established conversion ratios for conversion from other opioids to XTAMPZA ER defined by clinical trials</td>
<td></td>
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<tr>
<td><strong>Abuse Deterrence</strong></td>
<td>XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse</td>
</tr>
</tbody>
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<th>ZOHYDRO ER</th>
<th>Hydrocodone Bitartrate</th>
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<tr>
<td><strong>Key Instructions</strong></td>
<td></td>
</tr>
<tr>
<td>Opioid-naïve patients: initiate treatment with 10 mg every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Titrate using 5- to 7-day intervals</td>
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</tr>
<tr>
<td>Renal impairment (creatinine clearance &lt;60 mL/min): start with a low dose</td>
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<tr>
<td>Instruct patient: Swallow capsules whole</td>
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<td>DO NOT chew, crush, or dissolve</td>
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<td>CYP3A4 inhibitors may increase hydrocodone exposure</td>
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<td><strong>Use in Opioid-Tolerant Patients</strong></td>
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<td><strong>Relative Potency to Oral Morphine</strong></td>
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</tr>
<tr>
<td>Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio</td>
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