Key Opioid Label Updates

The following tables provide a comparison of the more significant label updates included in this action intended to provide additional guidance on prescribing opioid analgesics. These updates apply to opioid analgesics intended for use in the outpatient setting, although many also apply to opioid analgesics used in the inpatient setting. The below list is not exhaustive. These are representative examples of "former" and "new" labels. Other minor updates were incorporated within this action but are not listed below and will be available once the label updates for each product are approved by the FDA. Updated language is shown **in bold** and will be added to the Boxed Warning (Table 1), Indications and Usage (Tables 2 and 3), Dosage and Administration (Tables 4-7), Warnings and Precautions (Table 8), and Medication Guide (Table 9 - 11) sections of the opioid analgesic labels.

Table 1: Boxed Warning
(Applies to both Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics)

Former Order and Language	New Order and Updated (shortened) Language
Addiction, Abuse, and Misuse [TRADENAME] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing [TRADENAME] and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.X)]*. **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)** To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.X)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and • consider other tools to improve patient, household, and community safety. **Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression may occur with use of [TRADENAME]. Monitor for respiratory depression, especially during initiation of [TRADENAME] or following a dose increase *[see Warnings and Precautions (5.X)].* **Accidental Ingestion** Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in a fatal overdose of [active moiety] *[see Warnings and Precautions (5.X)]*. **Neonatal Opioid Withdrawal Syndrome**	**Addiction, Abuse, and Misuse** **Because the use of** [TRADENAME] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and **reassess** all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.X)]*. **Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression may occur with use of [TRADENAME], especially during initiation or following a dose increase. **To reduce the risk of respiratory depression, proper dosing and titration of** [TRADENAME] **are essential** *[see Warnings and Precautions (5.X)].* **Accidental Ingestion** (no change) Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in a fatal overdose of [active moiety] *[see Warnings and Precautions (5.X)]*. **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants** Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[*see *Warnings and Precautions (5.X), Drug Interactions (7)]*. **Neonatal Opioid Withdrawal Syndrome (NOWS)** **If opioid use is required for an extended period of time in a pregnant woman,** advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.X)]*. **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)** (also shortened)

Prolonged use of [TRADENAME] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.X)]*. **Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants** Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[*see *Warnings and Precautions (5.X), Drug Interactions (7)]*. • Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. • Limit dosages and durations to the minimum required. • Follow patients for signs and symptoms of respiratory depression and sedation.	Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.X)].*

Table 2: Indications and Usage *(Applies to Immediate-Release Opioid Analgesics)*	
Former	New
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.X)]*, reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products): • Have not been tolerated, or are not expected to be tolerated, • Have not provided adequate analgesia, or are not expected to provide adequate analgesia, or are not expected to provide adequate analgesia	**Limitations of Use:** Because of the risks of addiction, abuse, and misuse with opioids, **which can occur at any dosages or duration** *[see Warnings and Precautions (5.X)]*, reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products): • Have not been tolerated, or are not expected to be tolerated, • Have not provided adequate analgesia, or are not expected to provide adequate analgesia [TRADENAME] **should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.**

Table 3: Indications and Usage *(Applies to Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
[TRADENAME] is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. **Limitations of Use:** • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations *[see Warnings and Precautions (5.X)]*, reserve [TRADENAME] 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. • [TRADENAME] is not indicated as an as-needed (prn) analgesic.	[TRADENAME] is indicated for the management of **severe and persistent** pain **that requires an extended treatment period with a daily opioid analgesic** and for which alternative treatment options are inadequate. **Limitations of Use:** • Because of the risks of addiction, abuse, and misuse with opioids, **which can occur at any dosage or duration**, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, *[see Warnings and Precautions (5.X)]*, reserve [TRADENAME] 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. • [TRADENAME] is not indicated as an as-needed (prn) analgesic.

Table 4: Dosage and Administration **Important Dosage and Administration Instructions** *(Applies to Immediate-Release Opioid Analgesics)*	
Former	New
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].* Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.X)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with [TRADENAME] and adjust the dosage accordingly *[see Warnings and Precautions (5.X)].*	[TRADENAME] **should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.** Use the lowest effective dosage for the shortest duration **of time** consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. **Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of** [TRADENAME] **for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.** **Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.** **There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors.** Initiate the dosing regimen for each patient individually, taking into account the patient's **underlying cause and** severity of pain, prior analgesic treatment **and response**, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.X)]*. **Respiratory depression can occur at any time during opioid therapy, especially when** initiating and following dosage increases with [TRADENAME]. **Consider this risk when selecting an initial dose and when making dose adjustments** *[see Warnings and Precautions (5)].*

Table 5: Dosage and Administration **Initial Dosage** *(Applies to Immediate-Release Opioid Analgesics)*	
Former	New
Use of [TRADENAME] as the First Opioid Analgesic Initiate treatment with [TRADENAME] in a dosing range of X mg to X mg every Y to Y hours as needed for pain.	Use of [TRADENAME] as the First Opioid Analgesic Initiate treatment with [TRADENAME] in a dosing range of X mg to X mg every Y to Y hours as needed for pain, **at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of** [TRADENAME].

Table 6: Dosage and Administration **Important Dosage and Administration Instructions** *(Applies to Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
[TRADENAME] should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. … (product-specific information)… Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].* Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.X)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with [TRADENAME] and adjust the dosage accordingly *[see Warnings and Precautions (5.X)].*	[TRADENAME] should be prescribed only by healthcare professionals who are knowledgeable **about the use of extended-release/long-acting opioids and how to mitigate the associated risks.** … (product-specific information)… Use the lowest effective dosage for the shortest duration **of time** consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. **Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of** [TRADENAME] **for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.** Initiate the dosing regimen for each patient individually, taking into account the patient's **underlying cause and** severity of pain, prior analgesic treatment **and response**, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.X)]*. **Respiratory depression can occur at any time during opioid therapy, especially when** initiating and following dosage increases with [TRADENAME]. **Consider this risk when selecting an initial dose and when making dose adjustments** *[see Warnings and Precautions (5)].*

Table 7: Dosage and Administration **Initial Dosage** *(Applies to Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
Conversion from Other Opioids to [TRADENAME] Discontinue all other around-the-clock opioid drugs when [TRADENAME] therapy is initiated.	Conversion from Other Opioids to [TRADENAME] When [TRADENAME] therapy is initiated, discontinue all opioid **analgesics other than those used on an as needed basis for breakthrough pain when appropriate.**

Table 8: Warnings and Precautions *(Applies to <u>both</u> Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
(n/a)	**<u>5.X Opioid-Induced Hyperalgesia and Allodynia</u>** **Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)].* Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.** **Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety) *[see Dosage and Administration (2.X); Warnings and Precautions (5.X)]*.**

Table 9: Medication Guide *(Applies to Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
[TRADENAME] is: • A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them. • A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death. • Not for use to treat pain that is not around-the-clock	**[TRADENAME] is:** • A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage **severe and persistent** pain **that requires an extended treatment period with a daily opioid medicine**, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them. • A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death. • Not **to be taken on an "as needed" basis.**

Table 10: Medication Guide *(Applies to both Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics)*	
Former	New
Tell your healthcare provider if you: • **are pregnant or planning to become pregnant.** Prolonged use of [TRADENAME] during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.	**Tell your healthcare provider if you:** • **are pregnant or planning to become pregnant. Use of** [TRADENAME] **for an extended period of time** during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. • **notice your pain getting worse. If your pain gets worse after you take** [TRADENAME]**, do not take more of** [TRADENAME] **without first talking to your doctor. Talk to your doctor if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking** [TRADENAME].

Table 11: Medication Guide *(Applies to Immediate-Release Opioid Analgesics)*	
Former	New
When taking [TRADENAME]: • Do not change your dose. Take [TRADENAME]exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. • Take your prescribed dose every 4 to 6 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time. • Call your healthcare provider if the dose you are taking does not control your pain. • If you have been taking [TRADENAME] regularly, do not stop taking [TRADENAME] without talking to your healthcare provider. • Dispose of expired, unwanted, or unused [TRADENAME] by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.	**When taking [TRADENAME]:** • Do not change your dose. Take [TRADENAME]exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. • **For acute (short-term) pain, you may only need to take** [TRADENAME] **for a few days. You may have some** [TRADENAME] **left over that you did not use. See disposal information at the bottom of this section for directions on how to safely dispose of** [TRADENAME]**.** • Take your prescribed dose every 4 to 6 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time. • Call your healthcare provider if the dose you are taking does not control your pain. • If you have been taking [TRADENAME] regularly, do not stop taking [TRADENAME] without talking to your healthcare provider. • Dispose of expired, unwanted, or unused [TRADENAME] by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

NOTE: FDA defines *misuse* as the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed. FDA defines *abuse* as the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.