FDA Drug Safety Communication

FDA is requiring opioid pain medicine manufacturers to update prescribing information regarding long-term use

This class-wide action will further emphasize and characterize risks of long-term use to help patients and health care professionals make informed treatment decisions

07-31-2025 FDA Drug Safety Communication

What Safety Concern Is FDA Announcing?
In May 2025, the U.S. Food and Drug Administration (FDA) convened a joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to discuss two recently completed observational studies examining the risks of misuse, abuse, addiction, and fatal and non-fatal overdose in patients on long-term opioid analgesic (also referred to as opioid pain medicine) therapy. These studies (postmarketing requirements [PMR] 3033-1 and 3033-2) provided new, quantitative data on risks of these serious adverse outcomes in patients prescribed opioid pain medicines long term. After reviewing the study findings and the medical literature, as well as considering the committees' and public input, FDA has determined that this new information should be included in drug labeling to help health care professionals and patients better understand the benefit-risk profile of opioid pain medicines when prescribed long-term and to make more informed decisions. Separately, a prospective, randomized, controlled clinical trial will address a different PMR to examine the risks relative to the efficacy of long-term opioid use.

What Is FDA Doing?
The Agency is requiring safety labeling changes for opioid pain medicines to further emphasize and characterize the risks associated with long-term use. Specifically, FDA is notifying application holders the following labeling changes are needed:

- Remove the phrase "extended treatment period" in the Indications and Usage section to avoid misinterpretation that there are data to support safety and efficacy of opioid analgesics over an indefinitely long duration
- Further emphasize that higher doses are associated with increased risk of serious harm, and that the risks of serious harms persist over the course of therapy
- Provide a brief description of the results of studies conducted to fulfill postmarketing requirements 3033-1 and 3033-2, including new quantitative estimates of the risks of addiction, abuse, misuse, and fatal and non-fatal overdose in patients taking opioid analgesics long-term

FDA is also requiring labeling updates to further clarify that extended-release/long-acting opioid pain medicines should only be used when alternative therapies, including immediate-release opioid pain medicines, are inadequate to manage severe and persistent pain, and to emphasize the importance of avoiding rapid dose reduction or abrupt discontinuation in patients who may be physically dependent on opioid pain medicines.
Additionally, FDA is requiring labeling updates regarding the availability of opioid overdose reversal agents; revising drug-drug interactions with central nervous system depressants to include

gabapentinoids; adding information about toxic leukoencephalopathy (a neurological disorder due to a variety of causes, including exposure to toxic substances) in the opioid overdose setting; and modifying warnings about gastrointestinal effects to include opioid-induced esophageal dysfunction.

What Is an Opioid Pain Medicine and How Can It Help Me?
Opioid pain medicines are a class of powerful pain medicines prescribed to treat pain that does not respond well to other treatments, including non-opioid pain medicines. They activate an area of nerve cells in the brain and body that block pain signals. These medicines have benefits when used appropriately, but they also have serious risks, including misuse, abuse, addiction, overdose, and death. Examples of common opioid pain medicines include codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, fentanyl, buprenorphine, methadone, and tramadol.

What Should I Do as a Health Care Professional?
In assessing the severity of pain, discuss with the patient the source of the pain and the impact of the pain on their ability to function and their quality of life. Pain assessment should consider the cause of pain and individual patient factors and include non-pharmaceutical, non-interventional targeted treatments that address the root cause of the underlying pain, when possible. Use a multimodal approach to pain management when initiating treatment, throughout the course of therapy, and if you decide to taper or discontinue the opioid pain medicine.

If the patient's pain is severe enough to require an opioid pain medicine and alternative treatment options are insufficient, prescribe the lowest effective dose of an immediate-release (IR) opioid pain medicine for the shortest duration of time needed to reduce the risks associated with these products. Discuss what is known about the risks and benefits of using the medication. Reserve increasing to higher doses only when lower doses are inadequate and the benefits of using a higher dose outweigh the substantial risks. Many acute pain conditions, such as pain occurring with surgical procedures or musculoskeletal injuries, require no more than a few days of an IR opioid pain medicine. Remind the patient that opioid use can paradoxically increase pain (i.e., opioid-induced hyperalgesia).

Reserve extended-release/long-acting opioid pain medicines only for severe and persistent pain that cannot be adequately treated with alternative options, including IR opioid pain medicines. Regularly re-evaluate and discuss with your patients the optimum management of pain that seeks to address the root cause and appropriately balances the known benefits and risks, and frequently assess for development of addiction, abuse, or misuse. Inform patients and caregivers of the added risks of using opioid pain medicines with benzodiazepines and other central nervous system depressants, including gabapentinoids, and educate them on the signs and symptoms of respiratory depression.

For all patients prescribed opioid pain medicines, discuss opioid overdose reversal agents, such as naloxone and nalmefene. In March 2023, FDA approved the first nasal spray version of naloxone to be sold over-the-counter. There are now several versions of naloxone nasal sprays available over-the-counter, including generics, as well as versions available by prescription. In addition, in August 2024, FDA approved the first nalmefene hydrochloride auto-injector as a prescription drug to treat opioid overdose in adults and pediatric patients aged 12 years and older.

Regularly re-evaluate the benefit-risk profile for any individual taking opioid pain medicines for more than a few days. Be aware that overdose risk is increased with higher opioid pain medicine doses, and risks of serious harms persist over the course of therapy. If you determine opioid pain medicines are indicated, consider an IR opioid pain medicine as an as-needed, first-line treatment. Avoid rapidly reducing or abruptly discontinuing opioid pain medicines in patients who may be physically dependent on the medication because such changes have resulted in serious withdrawal symptoms, uncontrolled pain, and suicide.

What Should I Do as a Patient or Parent/Caregiver?
Always take your opioid pain medicine exactly as prescribed. Do not take more of the medicine or take it more often than prescribed without first talking to your health care professional. Talk with them if your pain increases, you feel more sensitive to pain, or if you have new pain, especially from touch or other things that are not usually painful such as combing your hair.

Store your opioid pain medicines securely, out of sight and reach of children and pets, and in a location not accessible by others, including home visitors. Do not share these medicines with anyone else, and immediately dispose of unused or expired opioid pain medicines or take them to a drug take-back site, location, or program. If provided, use the prepaid mail-back envelopes included with the prescription.

Seek emergency medical help or call 911 immediately if you or someone you are caring for experiences symptoms of respiratory problems, which can be life-threatening. Signs and symptoms include slowed, shallow, or difficult breathing, severe sleepiness, or not being able to respond or wake up.

Talk to your health care professionals about the benefits of naloxone and nalmefene, which can reverse an opioid overdose, and how to obtain these drugs. There are several versions of naloxone, some of which are available without a prescription. Nalmefene hydrochloride is available with a prescription from your health care professional.

Be aware that overdose risks are increased with higher opioid pain medicine doses and that the risks of serious harms persist over the course of therapy. Regularly visit your health care professional to ensure you are on the most appropriate treatment plan. Avoid rapidly reducing or abruptly discontinuing opioid pain medicine treatment without consulting a health care professional.

What Did FDA Find?
The labeling changes being announced today are based on the findings from observational studies conducted to fulfill two postmarketing requirements ([PMRs] 3033-1 and 3033-2) and the ensuing discussion at the May 2025 Advisory Committee meeting, alongside other data published in medical literature. The PMR studies — which were completed by the Opioid Postmarketing Consortium, a collaboration of all new drug application holders of extended-release/long-acting (ER/LA) opioid pain medicines — provided new, quantitative data on the risks of misuse, abuse, addiction, and fatal and non-fatal overdose for patients on long-term opioid pain medicine therapy.

PMR 3033-1 was a prospective, observational cohort study that estimated the risks of addiction, misuse , and abuse in patients initiating long-term use of Schedule II opioid analgesics (pain medicines). Patients were recruited and data collected from 2017 through 2021. Study participants had been enrolled in

selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, and either 1) filled multiple ER/LA opioid analgesic prescriptions during a 90-day period; or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days. Patients who received any of the qualifying opioid analgesics in the previous six months were excluded. Over 12 months, approximately 1-6% of included patients across the two cohorts newly met criteria for opioid addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Over 12 months, across the two cohorts, approximately 9% of included patients newly met criteria for prescription opioid abuse (i.e., the intentional use of a drug for a nontherapeutic purpose, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect) and approximately 22% newly met criteria for prescription opioid misuse (i.e., the intentional use of a drug for a therapeutic purpose inappropriately outside labeling directions or in a way other than prescribed or directed by a health care professional). Incidence of these outcomes varied according to patient- and drug-related factors, with the strongest and most consistent risk factor being a personal history of a substance use disorder.

PMR 3033-2 was a retrospective, observational cohort study that estimated the risk of opioid-involved overdose or opioid overdose-related death (together, abbreviated as OOD) in patients with new long-term use of Schedule II opioid analgesics between 2006 and 2016. Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least nine months. New long-term use was defined as having Schedule II opioid analgesic prescriptions covering at least 70-days' supply over the three months before study entry and none during the preceding six months. Patients were excluded if they had an opioid-involved overdose in the nine months before cohort entry. The outcome was the first OOD during the follow-up period, as measured using a validated medical code-based algorithm with linkage to the National Death Index database. The five-year cumulative incidence estimates for OOD ranged from approximately 1.5-4% across study sites. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Again, incidence varied according to patient- and drug-related factors, with higher baseline opioid dose being a strong and consistent risk factor for OOD. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies. Nonetheless, these new data may help inform the benefit-risk assessment in patients for whom long-term use of opioid analgesics is being considered. Additional details about PMRs 3033-1 and 3033-2 can be found in the "Background and Data Summary" section.

What Is My Risk?

Like all medicines, opioid pain medicines can have side effects, even when used correctly as prescribed. It is important to know that people respond differently to medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking opioid pain medicines. Talk to your health care professional if you have questions or concerns about the risks.

How Can I Report Side Effects from Opioid Pain Medicines?
To help FDA track safety issues, we urge patients and health care professionals to report side effects involving opioid pain medicines or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

How Can I Get New Safety Information on Medicines I'm Prescribing or Taking?
You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.

Table of Key Opioid Label Updates
[Included on pages 11-19 of this document]

Facts About Opioid Pain Medicines

- Opioid pain medicines are powerful prescription medicines that can help manage pain when other treatments and medicines are not able to provide enough relief. However, opioid pain medicines also carry serious risks, including misuse and abuse, addiction, overdose, and death.
- There are two main categories of prescription opioid pain medicines. Immediate-release (IR) products are usually intended for use every four to six hours as needed for acute pain. Extended-release/long-acting opioid pain medicines are intended to be taken only once or twice a day for severe and persistent pain that cannot be adequately treated with alternative options, including IR opioid pain medicines.
- Opioid pain medicines are available in many different forms, including tablets, capsules, lozenges, sublingual tablets, transdermal patches, nasal sprays, and injections.
- Common side effects include drowsiness, dizziness, nausea, vomiting, constipation, physical dependence, and slowed or difficult breathing.
- The risk of opioid addiction, misuse, or abuse is increased in patients with a personal or family history of substance use disorder or mental illness.
- Naloxone and nalmefene are opioid reversal medicines used to treat an opioid overdose or possible overdose and can help prevent death. Naloxone is available over-the-counter and by prescription; nalmefene hydrochloride is available by prescription only.

Additional Information for Health Care Professionals

- As part of its ongoing efforts to address the nation's opioid crisis and based, in part, on results of postmarketing requirement studies, FDA is requiring safety labeling changes to provide more information on the risks of opioid pain medicines.
- Health care professionals are reminded to regularly re-evaluate the benefit-risk profile for any individual taking opioid pain medication.
- Be aware that overdose risks are increased with higher opioid doses, and that the risks of serious harms persist throughout the course of therapy.
- If an opioid pain medicine is necessary, consider immediate-release opioid pain medicine as an as-needed, first-line treatment.
- Avoid rapidly reducing or abruptly discontinuing opioids in patients who may be physically dependent on the medication because such changes have resulted in serious withdrawal symptoms, uncontrolled pain, and suicide.

- For all opioid pain medicines, prescribe the lowest effective dose for the shortest duration consistent with a patient's individual treatment goals. Because the risk of overdose increases as opioid pain medicine dose increases, reserve titrating to higher doses for patients who have an inadequate response to lower doses and when the benefits of a higher dose clearly outweigh the substantial risks.
- Regularly reassess the continued need for opioid pain medicine use regardless of the dose and for signs of addiction, misuse, or abuse.
- Educate patients and caregivers that taking an opioid pain medicine other than how it is prescribed or with alcohol, benzodiazepines, or other central nervous system depressants (including gabapentinoids) could increase the risk of overdose, and how to recognize the signs and symptoms of respiratory depression.
- Naloxone and nalmefene are opioid reversal medicines used to treat an opioid overdose or possible overdose and can help prevent death. Naloxone is available over-the-counter and by prescription; nalmefene hydrochloride is available by prescription only.
- Encourage patients to read the patient Medication Guide they receive with their filled prescription(s). Important, new information may be included. The Medication Guide explains the important things they need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when they are taking the medicine.
- To help FDA track safety issues with medicines, report adverse events involving opioid pain medicines or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines and medical specialties of interest to you.

Additional Information for Patients/Caregivers

- Be aware of the risks of opioid pain medicine use, including misuse, abuse, addiction, overdose, and death.
- Regularly visit your health care professional to ensure you are on the most appropriate treatment plan for opioid pain medicines.
- Be aware that overdose risks are increased with higher opioid pain medicine doses, and that the risk of serious harm persists throughout the course of therapy.
- Avoid rapidly reducing your dose or abruptly discontinuing opioid pain medicines without consulting a health care professional.
- Always take opioid pain medicines as prescribed. Do not take more doses or take them more often than prescribed.
- For many acute pain conditions such as pain occurring with a number of surgical procedures or musculoskeletal injuries, you may only need to take opioid pain medicine for a few days. You may have some medicine left over that you did not use. Never give anyone else your opioid pain medicine. They could die from taking it. Selling or giving away your opioid pain medicine is against the law. Immediately dispose of unused or expired opioid pain medicines or take them to a drug take-back site, location, or program. See disposal information in the Medication Guide on how to safely dispose of your opioid pain medicine. If provided, use the prepaid mail-back envelopes included with the prescription. Unused medicines must be disposed of properly to

avoid harm. Visit www.fda.gov/drugdisposal to learn about how to properly dispose of unused medicine.

- Store your opioid pain medicines securely, out of sight and reach of children, and in a location not accessible by others, including visitors. Every year thousands of children are hospitalized, and some die, after taking medicine not meant for them. Millions of people misuse prescription opioid pain medicines each year, and thousands die from overdoses involving prescription opioid pain medicines.
- Signs of an opioid overdose include breathing problems, severe sleepiness, or not being able to respond or wake up. Seek medical attention immediately if you or someone you are caring for experiences these life-threatening symptoms.
- Naloxone and nalmefene are opioid reversal medicines used to treat an opioid overdose or possible overdose and can help prevent death. Naloxone is available over-the-counter and by prescription; nalmefene is available by prescription only. Talk to your health care professional about how to use these products.
- To help FDA track safety issues with medicines, report side effects from opioid pain medicines or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts about Drug Safety Communications on medicines and medical specialties of interest to you.

Background and Data Summary

Using its authority under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, FDA required extended-release/long-acting (ER/LA) opioid analgesic (OA) new drug application holders to conduct epidemiologic studies to 1) quantify the serious risks of misuse, abuse, addiction, and fatal and non-fatal overdose in patients using OAs long term and 2) assess potential risk factors for these outcomes. The studies were conducted using prespecified protocols and statistical analysis plans that were reviewed by FDA and discussed in a public scientific workshop. Studies conducted under postmarket requirements (PMRs) 3033-1 and 3033-2 were large, multisite investigations that included patients enrolled in various health insurance plans and health systems across the United States. These studies were, by design, restricted to the relatively small proportion of patients receiving OAs who go on to use them long term and therefore do not inform quantitative questions of risk related to shorter-term use of OAs.

PMR 3033-1 was a prospective, observational cohort study that estimated the risks of addiction, abuse, and misuse in adult patients initiating long-term use of Schedule II OAs. Patients were recruited and data were collected from 2017 through 2021. Study participants had been enrolled in selected health insurance plans or health systems for at least one year, and either 1) filled multiple ER/LA OA prescriptions during a 90-day period ("ER/LA cohort"); or 2) filled any Schedule II OA prescriptions covering at least 70 of 90 days ("long-term opioid therapy [LtOT] cohort"). Patients who received any of the qualifying opioid analgesics (i.e., ER/LA OAs or Schedule II OAs, depending on the study cohort) in the previous six months were excluded; however, patients were not excluded for use of other prescription OA therapy. In addition, patients with an existing diagnosis of a terminal illness or opioid use disorder (OUD) in the previous 12 months, receiving methadone or buprenorphine for the treatment of OUD, or receiving hospice care were excluded. Continued OA use was not required during follow-up. After meeting the study eligibility criteria, patients were required to be free of at least one outcome at

baseline and to have completed a minimum number of follow-up assessments (at least two of the three-, six-, nine-, and 12-month assessments for misuse and abuse; the 12-month assessment for OUD) to be included in one or more analyses. This resulted in 978 and 1,244 patients being included in one or more analyses for the ER/LA and LtOT cohorts, respectively.

Opioid misuse was defined as the intentional use of a drug for a therapeutic purpose inappropriately outside labeling directions or in a way other than prescribed or directed by a health care professional. Opioid abuse was defined as the intentional use of a drug for a nontherapeutic purpose, repeatedly or sporadically, or for the purpose of achieving a positive psychological or physical effect. Misuse and abuse were measured using the Prescription Opioid Misuse and Abuse Questionnaire, a self-reported questionnaire validated for use in this population, which asks about symptoms in the past three months. Over 12 months, across the two cohorts, approximately 22% of included patients newly met criteria for prescription opioid misuse and approximately 9% of included patients newly met criteria for prescription opioid abuse, based on information reported at three-, six-, nine-, and 12-month assessments (Table 1).

Addiction was defined in this study as moderate-to-severe OUD, as assessed using a validated, semi-structured interview tool, the Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version (PRISM-5-Op), which asks about symptoms in the past 12 months. OUD was based on a count of symptoms reported in the interview and defined in two ways: 1) using standard DSM-5 criteria, and 2) using modified criteria in which most DSM-5 symptoms were counted toward an OUD designation only when the patient indicated a non-pain reason for opioid use associated with that symptom, and the "persistent desire or attempts to quit or cut down on opioid use" criterion was counted only if multiple unsuccessful attempts were made. Over 12 months, across the two cohorts, the percentage of included patients who newly met criteria for moderate-to-severe OUD was approximately 3-6% using the standard DSM-5 criteria and approximately 1-2% using the modified DSM-5 criteria, based on information reported at the 12-month assessment (Table 1). Several factors (e.g., potential volunteer bias, predominance of managed care and integrated healthcare systems) may have limited the generalizability and interpretability of findings.

PMR 3033-2 was a retrospective, observational cohort study that estimated the risk of opioid-involved overdose or opioid overdose-related death (together, abbreviated as OOD) in adult patients with new long-term use of Schedule II OAs between 2006 and 2016 (n=220,249). The study included patients enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least nine months. New long-term use was defined as having Schedule II OA prescriptions[1] covering at least a 70-days' supply over the three months before cohort entry and none during the preceding six months. Patients were excluded if they had an opioid-involved overdose in the nine months prior to cohort entry. The outcome was the first OOD event during the follow-up period, as measured using a validated medical-code-based algorithm with linkage to the National Death Index database. The cumulative incidence of OOD increased steadily throughout the five-year follow up period, resulting in a five-year cumulative incidence ranging from approximately 1.5% to approximately 4% (Table 2). Over the entire study period (5-11 years, depending on study site), approximately 17% of first OOD events were fatal.

[1] Hydrocodone fixed combinations were reclassified from Schedule III to Schedule II in October 2014. Products containing hydrocodone were treated as a Schedule II opioid throughout PMR 3033-2.

There are a number of considerations when interpreting the findings from PMR 3033-2. OOD events may not have involved the prescribed OAs; rather, they could have occurred after a patient discontinued prescribed OA use and could have involved illicit opioids like heroin or fentanyl. Since the outcome for this study included only the first OOD event, a patient could have experienced subsequent events, including fatal overdose, that would not have been included in the OOD incidence estimates. Additionally, the intentionality of the OOD event (i.e., suicide vs. accidental) could not be adequately confirmed. Several factors could have contributed to bias. There was substantial attrition over the first five years of follow-up, and although this study used an incidence measure designed to account for loss to follow-up, if those who left the cohort (e.g., due to insurance disenrollment) systematically had a different risk of OOD than those remaining in the study, incidence estimates could have been biased. In addition, limiting the cohort to patients with no recent documente
d opioid-involved overdose likely selected patients at lower risk of OOD during follow-up. Finally, opioid overdoses that were reversed by a bystander or that otherwise did not result in either a medical claim or death were not captured.

Both studies collected patient- and drug-related characteristics at baseline and conducted exploratory analyses of potential risk factors for misuse, abuse, addiction, and overdose. Many factors were associated with one or more outcomes, with one of the strongest and most consistent risk factors being a personal history of a substance use disorder.[2] In addition, higher OA dose during the three months before cohort entry was a strong and consistent risk factor for OOD. Neither study was designed to assess associations between changes in OA dose or discontinuation of opioids and adverse opioid-related outcomes.

[2] A notable proportion of patients starting long-term OA therapy in these studies had a personal history of SUD, whether in the past year (in PMR 3033-1, 6.5% to 8% had a past-year non-opioid, non-nicotine substance use disorder, based on interview measures; in PMR 3033-2, approximately 4-6% each had OUD, alcohol use disorder, or another substance use disorder, based on diagnostic codes). PMR 3033-1 also assessed SUDs prior to the past year (29% to 34.1% had a prior-to-past-year non-opioid, non-nicotine substance use disorder, based on interview measures).

Table 1. Incidence of Prescription Opioid Misuse, Prescription Opioid Abuse, and OUD in Prospective PMR 3033-1

			Moderate-to-Severe OUD	
	Prescription Opioid Misuse	Prescription Opioid Abuse	Pain-Adjusted DSM-5-OUD[1]	DSM-5-OUD[2]
ER/LA cohort[3]				
N	804	911	850	850
12-month incidence proportion (%, 95% CI)	22.8 (21.6, 24.0)	9.4 (7.7, 11.6)	1.4 (0.9, 2.3)	5.8 (4.5, 7.3)
LtOT cohort[4]				
N	1,003	1,151	1,102	1,102
12-month incidence proportion (%, 95% CI)	21.6 (18.3, 25.5)	8.6 (7.4, 10.0)	1.6 (0.9, 2.9)	3.4 (2.5, 3.1)

Source: Adapted from Final Study Report for Prospective PMR 3033-1.

[1] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[2] Moderate-to-severe DSM-5 OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[3] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[4] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; N, number; OA, opioid analgesic; OUD, opioid use disorder; PMR, postmarketing requirement; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DMS-5, Opioid Version

Table 2. Cumulative Incidence of OOD in PMR 3033-2

	HealthCore	KPNW	Optum	VUMC
N	81,782	12,009	54,515	71,932
5-year cumulative incidence (%, 95% CI)[1]	1.5 (1.4, 1.6)	1.4 (1.2, 1.7)	1.5 (1.3, 1.8)	4.1 (3.9, 4.3)

Source: Adapted from the Final Study Report for PMR 3033-2.

[1] Five-year cumulative incidence is the complement of the Kaplan-Meier OOD-free survival preceding 5 years measured in percent (%) scale

Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; N, number; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; VUMC, Vanderbilt University Medical Center (Medicaid)

Section	Former Labeling Language	Changes (additions/changes in **bold underline**, deletions in ~~strikethrough~~)
HIGHLIGHTS OF PRESCRIBING INFORMATION		**Dosage and Administration** • **Periodically reassess patients receiving [TRADENAME] to evaluate the continued need for opioid analgesics to maintain pain control, the signs or symptoms of adverse reactions, and the development of addiction, abuse, or misuse. (2.x)**
	Dosage and Administration • Do not abruptly discontinue [TRADENAME] in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.x, 5.x)	• Do not **rapidly reduce or** abruptly discontinue [TRADENAME] in a physically dependent patient because rapid **reduction or abrupt** discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.x, 5.x)
BOXED WARNING	• If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, 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)]*	• ~~If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS,~~ **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome,** 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)]*.
1 INDICATIONS AND USAGE	***ER/LA Opioid Analgesics***	
	[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 (5.1)]*, 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 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~~ **that cannot be adequately treated with alternative options, including immediate-release opioids**. Limitations of Use • Because of the risks of addiction, abuse, ~~and~~ misuse**, overdose, and death** ~~with opioids~~, which can occur at any dosage or duration **and persist over the course of therapy** ~~and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations~~ *[see Warnings and Precautions (5.1)]*, reserve **opioid analgesics, including** [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.
	IR/SA Opioid Analgesics	

	Limitations of Use Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration *[see Warnings and Precautions (5.1)]*, 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.	Limitations of Use Because of the risks of addiction, abuse, ~~and~~ misuse**, overdose, and death** ~~with opioids~~, which can occur at any dosage or duration **and persist over the course of therapy** *[see Warnings and Precautions (5.1)]***,** reserve **opioid analgesics, including** [TRADENAME], for use in patients for whom alternative treatment options **are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.** ~~(e.g., non-opioid analgesics or non-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.~~
2 DOSAGE AND ADMINISTRA-TION	**2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose** Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with [TRADENAME] *[see Warnings and Precautions (5.x)]*. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.x, 5.x, 5.x)]*. Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.	**2.2 Patient Access to ~~Naloxone~~ an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose** *(Replace section text with the following language.)* **Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.x, 5.x, 5.x)]*.** **Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.x)]*.** **There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.**
	2.x Safe Reduction or Discontinuation of [TRADENAME] Do not abruptly discontinue [TRADENAME] in patients who	**2.x Safe Reduction or Discontinuation of [TRADENAME]** Do not **rapidly reduce or** abruptly discontinue [TRADENAME] in patients who may

	may be physically dependent on opioids.	be physically dependent on opioids.
		ER/LA Opioid Analgesics
	2.x Initial Dosing Use of [TRADENAME] as the First Opioid Analgesic (Opioid-Naïve Patients) *[drug-specific dosing instructions]*	**2.x Initial Dosing** ~~Use of [TRADENAME] as the First Opioid Analgesic (Opioid-Naïve Patients)~~ *Language regarding the use of an ER/LA opioid analgesic as the first opioid analgesic varies from product to product (an example is shown immediately above). This change, indicated by ~~strikeout~~ in this table, will apply to all language in ER/LA labeling on this topic. All existing language suggesting that a given ER/LA opioid analgesic can be used in opioid-naïve patients will be removed from labeling.*
5 WARNINGS AND PRECAUTIONS	**5.1 Addiction, Abuse, and Misuse** [TRADENAME] contains [drug], a Schedule II controlled substance. As an opioid, [TRADENAME] exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. Because extended-release products such as [TRADENAME] deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of [drug] present *[see Drug Abuse and Dependence (9)]*. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed [TRADENAME]. Addiction can occur at recommended dosages and if the drug is misused or abused.	**5.1 Addiction, Abuse, and Misuse** [TRADENAME] contains [drug], a Schedule II controlled substance. As an opioid, [TRADENAME] exposes users to the risks of addiction, abuse, and misuse. ~~Because extended-release products such as [TRADENAME] deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of [drug] present~~ *[see Drug Abuse and Dependence (9)]*. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed [TRADENAME]. Addiction can occur at recommended doses and if the drug is misused or abused. **The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.X)].***
	5.x Life-Threatening Respiratory Depression Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with [TRADENAME]. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers	**5.x Life-Threatening Respiratory Depression** Patient Access to ~~Naloxone~~ **an Opioid Overdose Reversal Agent** for the Emergency Treatment of Opioid Overdose **Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.x, 5.x)].*** **Discuss the options for obtaining an opioid overdose reversal agent (e.g.,**

	on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered. Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x), Overdosage (10)]*.	**prescription, over-the-counter, or as part of a community-based program).** **There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.** **Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x), Overdosage (10)].*** **5.x Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**
	5.x Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants Profound sedation, respiratory depression, coma, and death may result from concomitant use of [TRADENAME] with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepines, sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. … If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.x), Warnings and Precautions (5.x), Overdosage (10)]*.	**5.x Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants** Profound sedation, respiratory depression, coma, and death may result from concomitant use of [TRADENAME] with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepines, sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, **gabapentinoids**, and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. … If concomitant use is warranted, consider prescribing ~~naloxone for the emergency treatment of~~ **an** opioid overdose **reversal agent** *[see Dosage and Administration (2.x), Warnings and Precautions (5.x), Overdosage (10)]*.

	5.x Risk of Use in Patients with Gastrointestinal Conditions [TRADENAME] is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The [drug] in [TRADENAME] may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including pancreatitis, for worsening symptoms.	**5.x Risk of ~~Use in Patients with~~ Gastrointestinal ~~Conditions~~ Complications** [TRADENAME] is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The [drug] in [TRADENAME] may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including pancreatitis, for worsening symptoms. **Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate.**
6 ADVERSE REACTIONS	**6.X Postmarketing Experience** *(New section discussing PMR study results to be added)*	**6.X Postmarketing Experience** **Adverse Reactions from Observational Studies** **A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90 day period (n=978); or 2) filled any Schedule II opioid analgesic for at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months. Over 12 months:** • **approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and** • **approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse [defined in Drug Abuse and Dependence (9.2)], respectively, as measured with a validated self-reported instrument.** **A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs,**

one managed care program, or one Medicaid program for at least 9 months. New long-term use was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table X: Clinically Significant Drug Interactions with TRADENAME

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing ~~naloxone for the emergency treatment of~~ **an** opioid overdose **reversal agent** *[see Dosage and Administration (2.x, 2.x), Warnings and Precautions (5.x, 5.x, 5.x)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants,

	general anesthetics, antipsychotics, **gabapentinoids**, other opioids, alcohol.	

Muscle Relaxants	
Clinical Impact:	[Drug] may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of [TRADENAME] and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing ~~naloxone for the emergency treatment of~~ **an** opioid overdose **reversal agent** *[see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x)]*
Examples:	cyclobenzaprine, metaxalone

8 USE IN SPECIFIC POPULATIONS	Clinical Considerations *Labor or Delivery* Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate.	Clinical Considerations *Labor or Delivery* Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid ~~antagonist~~ **overdose reversal agent**, such as naloxone **or nalmefene**, must be available for reversal of opioid-induced respiratory depression in the neonate.
9 DRUG ABUSE AND DEPENDENCE	**9.3 Dependence** Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.	**9.3 Dependence** Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, **nalmefene**), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.
10 OVERDOSAGE	Clinical Presentation Acute overdose with [TRADENAME] can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Treatment of Overdose The opioid antagonists, such as naloxone, are specific antidotes	Clinical Presentation Acute overdose with [TRADENAME] can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. **Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.** Treatment of Overdose ~~The opioid antagonists, such as naloxone, are specific antidotes to respiratory~~

	to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.	~~depression resulting from opioid overdose.~~ For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid ~~antagonist~~ **overdose reversal agent such as naloxone or nalmefene**.
12 CLINICAL PHARMACOLOGY	**12.2 Pharmacodynamics** Effects on the Gastrointestinal Tract and Other Smooth Muscle Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.	**12.2 Pharmacodynamics** Effects on the Gastrointestinal Tract and Other Smooth Muscle Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, ~~and~~ transient elevations in serum amylase**, and opioid-induced esophageal dysfunction (OIED).**
17 PATIENT COUNSELING INFORMATION	Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with TRADENAME. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.x), Warnings and Precautions (5.x)]*. Educate patients and caregivers on how to recognize the signs and symptoms of an overdose. Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*. If naloxone is prescribed, also advise patients and caregivers: • How to treat with naloxone the overdose reversal agent in the event of an opioid overdose. • To tell family and friends about the naloxone opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency. • To read the Patient Information (or other educational material) that will come with their naloxone opioid	Patient Access to ~~Naloxone~~ **an Opioid Overdose Reversal Agent** for the Emergency Treatment of Opioid Overdose ~~Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with TRADENAME. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.x), Warnings and Precautions (5.x)]*.~~ **Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.** **Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Dosage and Administration (2.x), Warnings and Precautions (5.x)]*.** Educate patients and caregivers on how to recognize the signs and symptoms of an overdose. Explain to patients and caregivers that ~~naloxone's~~ effects **of opioid overdose reversal agents like naloxone and nalmefene** are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if ~~naloxone~~ **an opioid overdose reversal agent** is administered *[see Overdosage (10)]*. ~~If naloxone is prescribed, also a~~**A**dvise patients and caregivers:

	overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.	• ~~H~~ **h**ow to treat with ~~naloxone~~ **the overdose reversal agent** in the event of an opioid overdose. • ~~T~~ **t**o tell family and friends about the ~~naloxone~~ **opioid overdose reversal agent,** and to keep it in a place where family and friends can access it in an emergency. • ~~T~~ **t**o read the Patient Information (or other educational material) that will come with their ~~naloxone~~ **opioid overdose reversal agent**. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.
MEDICATION GUIDE	**Important information about TRADENAME:** • **Get emergency help or call 911 right away if you take too much [TRADENAME] (overdose).** When you first start taking [TRADENAME], when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose. • Taking [TRADENAME] with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.	**Important information about TRADENAME:** • **Get emergency help or call 911 right away if you take too much [TRADENAME] (overdose).** When you first start taking [TRADENAME], when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. ~~Talk to~~ **Ask** your healthcare provider about **medicines like** naloxone **or nalmefene that can be used in an emergency to reverse an opioid overdose.**~~, a medicine for the emergency treatment of an opioid overdose.~~ • Taking [TRADENAME] with other opioid medicines, benzodiazepines, **gabapentinoids (gabapentin or pregabalin),** alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.