



NDA

SAFETY LABELING CHANGE NOTIFICATION

APPLICANT NAME
ADDRESS

Attention: CONTACT NAME
TITLE

Dear CONTACT:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROPRIETARY NAME (ESTABLISHED NAME) DOSAGE FORM.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since DRUG was approved on DATE, we have become aware that certain patients are at an elevated risk of opioid overdose, such as those prescribed benzodiazepines or other central nervous system depressants concomitantly with opioids^{1,2,3}; those with a history of opioid use disorder (OUD)^{4,5}; and those who have had a prior opioid overdose.⁶ We have also become aware that increasing access to FDA-approved naloxone for some patients at elevated risk may help reduce their risk of fatal opioid overdose.⁷ Regardless of the patient's apparent risk, naloxone may be warranted to reduce risk of fatal overdose in their close contacts who may also be at elevated risk of

¹ Dasgupta N, Funk M, Proescholdbell S, Hirsch A, Ribisl K, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med* 2015. Doi: 10.1111/pme.12907.

² Park T, Saitz R, Ganoczy D, Ilgen M, Bohnert A. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ* 2015;350:h2698.

³ Myhre M, Diep L and Stubhaug A. Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanil. *Anesthesiology* 2016; 124: 141-149.

⁴ Kinsky S, Houck PR, Mayes K, et al. A comparison of adherence, outcomes, and costs among opioid use disorder Medicaid patients treated with buprenorphine and methadone: A view from the payer perspective. *Journal of Substance Abuse Treatment*. 2019; 104: 15-21.

⁵ Bohnert ASB, Ilgen MA, Ignacio RV, et al. Risk of Death From Accidental Overdose Associated With Psychiatric and Substance Use Disorders. *American Journal of Psychiatry*. 2012; 169:64 –70.

⁶ Larochelle MR, Bernson D, Land T, et al. Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. *Annals of Internal Medicine* 2018;169(3):137-145.

⁷ Walley AY, Doe-Simkins M, Quinn E, et al. Opioid overdose prevention with intranasal naloxone among people who take methadone. *Journal of Substance Abuse Treatment*. 2013;44(2):241-247.

opioid overdose (including children in the home at risk of accidental ingestion).^{8,9,10,11,12,13} We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and discussions held at the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee on December 17-18, 2018,¹⁴ regarding the potential benefit for patients of discussing with their healthcare provider their risk factors for opioid overdose and their need for access to naloxone, we believe that the new safety information should be included in the labeling for opioid analgesic products used in the outpatient setting and products approved for medication-based treatment of OUD as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

Insert the following bullet after all of the bullets referencing 2.x Important Dosage and Administration Instructions:

- Discuss availability of naloxone with the patient and caregiver and assess each patient’s need for access to naloxone, both when initiating and renewing treatment with TRADENAME. Consider prescribing naloxone based on the patient’s risk factors for overdose [2.x, 5.x, 5.x, 5.x].

⁸ Katzman JG, Takeda MY, Bhatt SR, et al. An Innovative Model for Naloxone Use Within an OTP Setting: A Prospective Cohort Study. *Journal of Addiction Medicine*. 2018;12(2):113-118

⁹ Katzman JG, Greenberg NH, Takeda MY, et al. Characteristics of Patients With Opioid Use Disorder Associated With Performing Overdose Reversals in the Community: An Opioid Treatment Program Analysis. *Journal of Addiction Medicine*. 2019; 13(2):131-138

¹⁰ Walley AY, Doe-Simkins M, Quinn E, et al. Opioid overdose prevention with intranasal naloxone among people who take methadone. *Journal of Substance Abuse Treatment*. 2013;44(2):241-247.

¹¹ Dwyer KH, Walley AY, Sorensen-Alawad A, et al. Opioid Education and Nasal Naloxone Rescue Kit Distribution in the Emergency Department. *Annals of emergency medicine*. 2013;62(4):S123-S123

¹² Gaither J, Leventhal J. National Trends in Hospitalizations for Opioid Poisonings Among Children and Adolescents, 1997 to 2012. *JAMA Pediatr*. October 2016

¹³ Khan NF, Bateman BT, Landon JE, Gagne JJ. Association of Opioid Overdose with Opioid Prescriptions to Family Members. *JAMA Intern Med*. epublished ahead of print June 24, 2019.
doi:10.1001/jamainternmed.2019.1064

¹⁴ U.S. Food and Drug Administration. Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. December 2018.

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FULL PRESCRIBING INFORMATION

For the following new labeling text, update the subsection numbering, the table of contents, and any cross references, as appropriate.

2 DOSAGE AND ADMINISTRATION

*Insert the following as a new subsection after **2.x Important Dosage and Administration Instructions**. Because this is a new subsection, format the heading [i.e., bold text] and adjust the subsequent numbering accordingly.*

2.x 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), Patient Counseling Information (17)*].

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.

5 WARNINGS AND PRECAUTIONS

5.x Addiction, Abuse, and Misuse

*At the end of the following paragraph, add a new sentence regarding consideration of prescribing naloxone as shown below. For clarity and context, new language is indicated by **bold, underlined** text.*

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing TRADENAME, and monitor all patients receiving TRADENAME for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of

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pain in any given patient. Patients at increased risk may be prescribed opioids such as TRADENAME, but use in such patients necessitates intensive counseling about the risks and proper use of TRADENAME along with intensive monitoring for signs of addiction, abuse, and misuse. **Consider prescribing naloxone for the emergency treatment of opioid overdose [see Dosage and Administration (2.x), Warnings and Precautions (5.x)].**

5.x Life-Threatening Respiratory Depression

*Add the new labeling text regarding educating patients and caregivers to recognize respiratory depression as follows. For clarity and context, new language is indicated by **bold, underlined** text.*

Accidental ingestion of even one dose of TRADENAME, especially by children, can result in respiratory depression and death due to an overdose of MOIETY.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see Patient Counseling Information (17)].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see Dosage and Administration (2.x)].

Additionally, at the end of this subsection, add new text as follows. The heading Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose, should be underlined as this information is a heading under this subsection.

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 on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see *Patient Counseling Information (17)*].

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 *Warnings and Precautions (5.x, 5.x), Patient Counseling Information (17)*].

5.x Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

*Insert a paragraph regarding consideration of prescribing naloxone as shown below. For clarity and context, new language is indicated by **bold, underlined** text.*

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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)*].

7 DRUG INTERACTIONS

*Insert the following language in the drug interaction table under "Intervention" for **Benzodiazepines and Other Central Nervous System (CNS) Depressants, and Muscle Relaxants**, as shown below. For clarity and context, new language is indicated by **bold, underlined** text.*

Table X: Clinically Significant Drug Interactions with TRADENAME

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	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 opioid overdose [see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x, 5.x)].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Muscle Relaxants	
<i>Clinical Impact:</i>	MOIETY may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	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 opioid overdose [see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x)].
<i>Examples:</i>	cyclobenzaprine, metaxalone

10 OVERDOSAGE

*Make the following revisions to the second paragraph under the header, Treatment of Overdose as follows. For clarity and context, deletions are indicated by strikeout and additions are **bolded, and underlined**.*

The Opioid antagonists, such as naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to TRADENAME overdose.

17 PATIENT COUNSELING INFORMATION

*Add a new paragraph regarding educating patients and caregivers on recognizing respiratory depression as shown below. For clarity and context, deletions are indicated by strikethrough and new language is indicated by **bold**, underlined text.*

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting TRADENAME or when the dosage is increased, and that it can occur even at recommended dosages [see ~~Warnings and Precautions (5.x)~~].

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see Warnings and Precautions (5.x)].

Add the following as a new header after Life-Threatening Respiratory Depression.

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 in the event of an opioid overdose
- To tell family and friends about their naloxone 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. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

MEDICATION GUIDE

The new text added below is underlined for ease of reference, but should not be underlined in the final Medication Guide. Deleted text is indicated by strikethrough.

Under the section: Important information about TRADENAME:, add “or call 911” and the new sentence at the end of the first bullet as shown below:

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.

Under the section: Before taking TRADENAME, tell your healthcare provider if you have a history of:, revise the last bullet as shown below:

Before taking TRADENAME, tell your healthcare provider if you have a history of:

- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Under the section: Tell your healthcare provider if you are:, add the following new bullet after the bullet regarding breastfeeding.

Tell your healthcare provider if you are:

- living in a household where there are small children or someone who has abused street or prescription drugs

Revise the following heading: Get emergency medical help if you have:, by adding, “or call 911 right away,” as shown below:

Get emergency medical help or call 911 right away if you have:

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

FDA intends to approve a labeling change common to all class members on the same day. In accordance with this policy, we have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end by February 17, 2021, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL
SUPPLEMENT**

OR

**SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT
WARRANTED).**

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT**

We remind you that requirements under section 505(o)(4) also apply to any authorized generic products marketed under this NDA.

If you have any questions, call LCDR Jessica Voqui, PharmD, MS; Safety Regulatory Project Manager, at ####-####-####.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director (Acting)
Division of Anesthesiology, Addiction Medicine,
and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research