



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 remifentanyl. *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 labeling text as a new bullet above the bullet regarding precipitating withdrawal and adjust cross reference numbers of the remaining items under this section header appropriately:

- Strongly consider prescribing naloxone at the time TRADENAME is initiated or renewed because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose. (2.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*. published 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.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

FULL PRESCRIBING INFORMATION

For the following new labeling text, update the subsection numbering within the text, 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. Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with TRADENAME. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose [see *Warnings and Precautions (5.x)*].

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with TRADENAME itself. Higher than normal doses and repeated administration of naloxone may be necessary due to the long duration of action of ESTABLISHED NAME and its affinity for the mu receptor [see *Overdosage (10)*].

Inform patients and caregivers of their options for obtaining 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 *Patient Counseling Information (17)*].

5 WARNINGS AND PRECAUTIONS

5.x Risk of Life-Threatening Respiratory and Central Nervous System (CNS) Depression

*Add the new labeling text as a new paragraph immediately before the paragraph regarding sleep-related breathing disorders as follows. For clarity and context, new language is indicated by **bold, underlined** text.*

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. Because Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose is a subheading, underline this text.

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.

Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with TRADENAME. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose [see *Dosage and Administration (2.x)*].

Advise patients and caregivers that naloxone may also be administered for a known or suspected overdose with TRADENAME itself. Higher than normal doses and repeated administration of naloxone may be necessary due to the long duration of action of TRADENAME and its affinity for the mu receptor [see *Overdosage (10)*].

Inform patients and caregivers of their options for obtaining 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, if naloxone is prescribed, how to treat with naloxone. Emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see *Patient Counseling Information (17)*].

5.x Managing Risks from Concomitant Use of 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.

For patients in TRADENAME treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's TRADENAME treatment and coordinate care to minimize the risks associated with concomitant use.

If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in TRADENAME treatment for opioid use disorder [see 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. 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 effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	<p>Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.</p> <p>Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments [see <i>Warnings and Precautions (5.x, 5.x)</i>].</p>

	<u>If concomitant use is warranted, strongly consider prescribing naloxone for the emergency treatment of opioid overdose, as is recommended for all patients in treatment for opioid use disorder [see Warnings and Precautions (5.x)].</u>
<i>Examples:</i>	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids.

Muscle Relaxants	
<i>Clinical Impact:</i>	TRADENAME may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients receiving muscle relaxants and TRADENAME 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. <u>Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, strongly consider prescribing naloxone for the emergency treatment of opioid overdose [see Dosage and Administration (2.x), Warnings and Precautions (5.x, 5.x)].</u>

17 PATIENT COUNSELING INFORMATION

Safe Use

Add the following new labeling text after the second bullet as two new bullets. Underline the bullet title for Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose.

- 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)*].
- Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Because patients being treated for opioid use disorder are at risk for relapse, discuss the importance of having access to naloxone with the patient and caregiver. Also discuss the importance of having access to naloxone if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Inform patients and caregivers of the options for obtaining 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 the signs and symptoms of an opioid 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. Repeat administration may be necessary, particularly for overdose involving TRADENAME, because naloxone is often not effective at the doses available for patient access [*Dosage and Administration (2.x)*, *Warnings and Precautions (5.x)*, *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 easily 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:** add “or call 911” and the new sentence at the end of the paragraph as shown below:*

IMPORTANT:

Keep TRADENAME in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses TRADENAME get emergency help or call 911 right away. Tell your healthcare provider if you are living in a household where there are small children.

*Under the section: **What is the most important information I should know about TRADENAME?**, revise the first bullet as follows:*

What is the most important information I should know about TRADENAME?

- ~~[MOIETY]~~ is a medicine in TRADENAME contains a medicine called ESTABLISHED NAME. ESTABLISHED NAME is an opioid that can cause serious and life-threatening problems, especially if you take or use certain other medicines or drugs.

Under the same section, add the following as the second bullet:

- Talk to your healthcare provider about naloxone. Naloxone is a medicine that is available to patients for the emergency treatment of an opioid overdose, including accidental use of TRADENAME by a child.

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