



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).

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product.

Since [TRADENAME] was approved on DATE, FDA has become aware of information derived from peer-reviewed publications^{1,2,3,4,5,6} that should be included in the labeling of opioid analgesics regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioid analgesics and benzodiazepines or other central nervous system depressants, including alcohol.

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, we believe that the following information should be included in the labeling for opioid analgesics:

¹ Jones C, McAninch J. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med* 2015;49(4):493–501.

² 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.

³ 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.

⁴ Jones C, Paulozzi L, Mack K. Alcohol Involvement in Opioid Pain Reliever and Benzodiazepine Drug Abuse-Related Emergency Department Visits and Drug-Related Deaths – United States, 2010. *MMWR* 2014;63(40):881-5.

⁵ Hwang C, Kang E, Kornegay C, Staffa J, Jones C, McAninch J. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. *Am J Prev Med* 2016. doi:10.1016/j.amepre.2016.02.014, Epub 2016 Apr 11.

⁶ Jones C, Mack K, Paulozzi L. Pharmaceutical overdose deaths, United States, 2010. *JAMA* 2013;309(7):657-9.

BOXED WARNING

[The following warning should be placed in the existing Boxed Warning as the last component.]

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.X)*, *Drug Interactions (7.X)*].

- **Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

5 WARNINGS AND PRECAUTIONS

[The following subsection should replace **5.X Risks due to Interactions with Central Nervous System Depressants**.]

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

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of [TRADENAME] with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see *Drug Interactions (7)*].

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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when [TRADENAME] is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see *Drug Interactions (7)* and *Patient Counseling Information (17)*].

7 DRUG INTERACTIONS

[The following subsection should replace **Central Nervous System (CNS) Depressants** in the Drug Interactions table.]

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, increases the risk of 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 [see <i>Warnings and Precautions (5.X)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

17 PATIENT COUNSELING INFORMATION

(for non-parenteral products) [The following subsection should replace Interactions with Alcohol and Other CNS Depressants.]

(for parenteral products)[The following subsection should replace Interactions with CNS Depressants.]

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if [TRADENAME] is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see *Warnings and Precautions (5.X)*, *Drug Interactions (7)*].

(for non-parenteral products only)

MEDICATION GUIDE

[Under **Important information about [TRADENAME]**, add the following text as the *second* bullet]

- Taking [TRADENAME] with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

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. **Alternatively, we encourage you to submit an amendment to supplement S-0xx, dated Month DD, YYYY.**

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 December 2, 2016, 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) – AMENDMENT

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

If you do not submit electronically, please send 5 copies of the submission.

(for non-parenteral products only)

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

If you have any questions, call Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research