



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) [formulation].

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 [formulation] 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 cough medications regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioids 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 cough medications as follows (additions shown in underline and deletions in strikethrough):

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, Ribis I 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

WARNING: 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 (5.1), Drug Interactions (7.1)]. Avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Concomitant use of opioids, including TRADENAME, with benzodiazepines, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Because of these risks, avoid use of opioid cough medications in patients taking benzodiazepines, other CNS depressants, or alcohol [see Drug Interactions (7.1)].

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacologic properties, it is reasonable to expect similar risk with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.

Advise both patients and caregivers about the risks of respiratory depression and sedation if TRADENAME is used with benzodiazepines, alcohol, or other CNS depressants [see Patient Counseling Information (17)].

7 DRUG INTERACTIONS

7.1 Benzodiazepines, Opioids, Antihistamines, Antipsychotics, Anti-anxiety Agents, or Other CNS Depressants (Including Alcohol)

The use of benzodiazepines, opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with [TRADENAME] may cause an additive CNS depressant effect, profound sedation, respiratory depression, coma, and death and should be avoided [see Warnings and Precautions (5.1)].

17. PATIENT COUNSELING INFORMATION

Replace the current language with the following:

Interactions with Benzodiazepines and Other Central Nervous System Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if [TRADENAME] is used with benzodiazepines or other CNS depressants, including alcohol. Because of this risk, patients should avoid concomitant use of [TRADENAME] with benzodiazepines or other CNS depressants, including alcohol [see *Warnings and Precautions (5.1), Drug Interactions (7.1)*].

We are also requiring a Medication Guide. See attachment for template.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement 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. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

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) – CHANGES BEING EFFECTED

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.

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 Carol Hill, Safety Regulatory Project Manager, at 301-796-1226.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research