



NDA #####

**SAFETY LABELING CHANGE NOTIFICATION  
PRIOR APPROVAL SUPPLEMENT REQUEST:  
UPDATE LABELING AND VOLUNTARY  
PHYSICIAN LABELING RULE (PLR) FORMAT**

COMPANY NAME  
STREET  
CITY, STATE ZIP CODE

Attention: COMPANY CONTACT

Dear COMPANY CONTACT:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [TRADENAME] (established name) tablets.

**SAFETY LABELING CHANGE**

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.

**MISUSE, ABUSE, ADDICTION, OVERDOSE, DEATH, and NEONATAL OPIOID  
WITHDRAWAL SYNDROME**

In April 2014, the product labeling of the class of extended-release and long-acting (ER/LA) opioid analgesics was updated to add more prominent warnings about the risks of misuse, abuse, addiction, overdose, death, and neonatal opioid withdrawal syndrome (NOWS). These products' indications were changed to better convey the patient population for whom the benefits of ER/LA opioid analgesics outweigh the risks. FDA has determined that similar changes are needed for immediate-release (IR) opioids.

Since [TRADENAME] was approved on August 31, 2000, we have become aware of two recent publications that provide evidence of persistent abuse and overdose mortality associated with IR

opioid products.<sup>1,2</sup> An additional study documented cases of neonatal abstinence syndrome<sup>3</sup> (NAS) occurring in infants born to mothers who were dispensed IR opioid products during pregnancy.<sup>4</sup>

The Cassidy and Johnson studies directly document that the use of IR opioid analgesics is associated with abuse, overdose, and death. These risks do not exist in isolation, however. Abuse can give rise to addiction and vice versa; for example, the Cassidy study on abuse includes a cohort of individuals who are already in treatment for addiction, thus illustrating the linkage between the two risks. In many cases, overdose and death are the result of misuse and abuse.<sup>5</sup> Given the interrelated nature of these risks (misuse, abuse, addiction, overdose, and death), the Cassidy and Johnson studies support an understanding that the risks of misuse and addiction also continue to contribute to the significant public health burdens associated with IR opioid analgesic use. Thus, these data and data analyses satisfy the statutory standard for “new safety information” as “information derived from . . . peer-reviewed biomedical literature. . . or other scientific data deemed appropriate by the [Agency]” about the serious risks of misuse, abuse, addiction, overdose, and death associated with the use of IR opioid analgesics.<sup>6</sup>

#### SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS

Since [TRADENAME] was approved on August 31, 2000, we have become aware of publications<sup>7,8</sup> in the medical literature describing the occurrence of serotonin syndrome following the initiation of an opioid in patients who had previously been taking one or more serotonergic drugs. Most frequently, the product implicated was one of the phenylpiperidine or diphenylheptane opioids (e.g., fentanyl, meperidine, methadone), but cases have been reported as well with other opioids (e.g., oxycodone). A search of FDA’s Adverse Event Reporting System also identified cases similar to those described in the published literature.

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<sup>1</sup> Cassidy TA, DasMahaptra P, Black RA et al. (2014) Changes in prevalence of Prescription Opioid Abuse after Introduction of an Abuse-Deterrent Opioid Formulation. *Pain Medicine*, 15: 440-451.

<sup>2</sup> Johnson H, Paulozzi L, Porucznik C et al. Decline in Drug Overdose Deaths After State Policy Changes – Florida, 2010-2012. Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report*, 63 (26), Published July 4th, 2014: 569-574.

<sup>3</sup> The term “neonatal abstinence syndrome” is a term used frequently in the medical literature that encompasses “neonatal opioid withdrawal syndrome (NOWS)” as well neonatal withdrawal from other drugs (e.g., benzodiazepines, selective serotonin reuptake inhibitors).

<sup>4</sup> Patrick SW, Dudley, J, Martin PR et al. (2015) Prescription opioid epidemic and infant outcomes. *Pediatrics*, 135 (5): 842-850.

<sup>5</sup> We note that there is not yet a generally accepted definition of “misuse,” although one purpose of the ER/LA opioid analgesic post-marketing studies FDA required in September 2013 (see September 10, 2013 Letter to ER/LA Opioid Analgesic NDA Holders (available at

<http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf>) is to facilitate the creation of such a definition. Thus, some studies may use the terms “abuse” and “misuse” interchangeably.

<sup>6</sup> See section 505-1(b)(3) of the FD&C Act.

<sup>7</sup> Rastogi R, Swarm RA, Patel TA. Case Scenario: Opioid Association with Serotonin Syndrome. *Anesthesiology* 2011; 115(6): 1291-8.

<sup>8</sup> Altman CS, Jahangiri MF. Serotonin Syndrome in the Perioperative Period. *Anesthesia and Analgesia* 2010; 110(2): 526-8.

### ADRENAL INSUFFICIENCY

Since [TRADENAME] was approved on August 31, 2000, we have become aware of publications<sup>9,10</sup> in the medical literature describing the occurrence of adrenal insufficiency in patients following the initiation of an opioid, more often following opioid use of greater than one month. Additionally, we have become aware of cases submitted to the FDA's Adverse Event Reporting System (FAERS) similar to those described in the published literature. Presentation of adrenal insufficiency included non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. In many cases, treatment with replacement corticosteroids was reported. A small number of cases reported reoccurrence of adrenal insufficiency when patients who recovered were rechallenged with the opioid they had been taking previously.

### ANDROGEN DEFICIENCY

Since [TRADENAME] was approved on August 31, 2000, we have become aware of publications in the medical literature describing androgen deficiency in patients with long-term exposure to opioids.<sup>11,12</sup> There are also published mechanistic studies that support the biological plausibility of opioid administration affecting gonadal hormone production through the suppression of pulsatile gonadotropin-releasing hormone by the hypothalamus.<sup>13,14</sup>

We consider all of the information described above 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, the following information should be included in the labeling for the class of IR opioid products, of which [TRADENAME] is a member. Generally, the revised text described below and attached in the labeling template should replace any existing labeling language on that topic in your current labeling.

Note that the following list includes the required safety labeling changes only and does not reflect the full text of product labeling. The cross references may require adjustment in your final product labeling.

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<sup>9</sup> Debono M, Chan S, Rolfe C, et al. Tramadol-induced adrenal insufficiency. *Eur J Clin Pharmacol* 2011; 67:865–7.

<sup>10</sup> Oltmanns KM et al. Chronic fentanyl application induces adrenocortical insufficiency. *Journal of Internal Medicine* 2005;257:478–80.

<sup>11</sup> Bhasin S, et al. Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2010; 95:2536– 2559.

<sup>12</sup> Daniell HW. Opioid endocrinopathy in women prescribed sustained-action opioids for control of nonmalignant pain. *J of Pain* 2008; 9:28-36.

<sup>13</sup> Kalra PS, et al. Opiate-induced hypersensitivity to testosterone feedback: pituitary involvement. *Endocrinology* 1988; 122:997-1003, 1988.

<sup>14</sup> Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain* 2009; 25:170-175.

## HIGHLIGHTS

- Addition of a **BOXED WARNING** to include information about Addiction, Abuse, and Misuse, Life-threatening Respiratory Depression, Accidental Ingestion, Neonatal Opioid Withdrawal Syndrome, and, as appropriate, significant drug product-specific interactions that would potentiate the opioid adverse effects. See Full Prescribing Information below.
- Full text from the **INDICATIONS AND USAGE** section of the Full Prescribing Information (plus the required pharmacological class).
- The addition of the following to **DOSAGE AND ADMINISTRATION**:
  - Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
  - Initiate treatment with (insert initial dosing regimen). (2.2)
  - (Insert summary of product-specific conversion information that is based upon your data, if available.)
  - Do not stop [TRADENAME] abruptly in a physically dependent patient. (2.X)
- The addition of the following to **CONTRAINDICATIONS**:
  - Significant respiratory depression. (4)
  - Acute or severe bronchial asthma in an unmonitored setting in absence of resuscitative equipment. (4)
- The addition of the following to **WARNINGS AND PRECAUTIONS**:
  - Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, and Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.X)
  - Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.X)
- The addition of the following under **DRUG INTERACTIONS**:
  - Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If co-administration is required, consider dose reduction of one or both drugs because of additive pharmacological effects and monitor closely.(5.X, 7)
  - Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue [TRADENAME] if serotonin syndrome is suspected. (7)

## FULL PRESCRIBING INFORMATION

- Addition of a **BOXED WARNING** to include information about Addiction, Abuse, and Misuse, Life Threatening Respiratory Depression, Accidental Ingestion, Neonatal Opioid Withdrawal Syndrome, and, as appropriate, significant drug product-specific interactions that would potentiate the opioid adverse effects.
- Modifications to the **INDICATIONS AND USAGE** section that make clear that this class of drugs is to be reserved for management of pain severe enough to require an opioid analgesic and for which alternative treatment options (e.g., non-opioid analgesics or opioid combination products) are inadequate because they have not been or are not expected to be tolerated or have not provided or are not expected to provide adequate analgesia.

- Modifications to the **DOSAGE AND ADMINISTRATION** section that include clearer instructions regarding patient monitoring, and drug administration, including initial dosage, dosage modifications, titration and maintenance of therapy, and discontinuation.
- Modification of **CONTRAINDICATIONS** to include:
  - Significant respiratory depression [*see Warnings and Precautions (5.X)*]
  - Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.X)*]
- Modification to **WARNINGS AND PRECAUTIONS** to include the following subsections:
  - Addiction, Abuse, and Misuse
  - Life-Threatening Respiratory Depression
  - Neonatal Opioid Withdrawal Syndrome
  - (if applicable) Significant drug product-specific interactions that would potentiate opioid effects.
  - Risks Due to Interactions with Central Nervous System Depressants
  - Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
  - Adrenal Insufficiency
- Addition to **ADVERSE REACTIONS** to include a list of serious adverse reactions described under **WARNINGS AND PRECAUTIONS**
- Addition of serotonin syndrome and adrenal insufficiency to the Postmarketing Experience subsection of **ADVERSE REACTIONS**
- Addition of a statement about androgen deficiency to the Postmarketing Experience subsection of **ADVERSE REACTIONS**
- Modification to the **DRUG INTERACTIONS** section to include the following subsections:
  - Significant drug product-specific interactions that would potentiate opioid effects
  - Central Nervous System (CNS) Depressants
  - Serotonergic Drugs
- Modification to the **USE IN SPECIFIC POPULATIONS** section to include specific information about NOWS and the potential for neonatal respiratory depression during delivery or with breast feeding; the potential risk for infertility with chronic opioid use; and the greater risk of respiratory depression in the elderly.
- Modification to the **DRUG ABUSE AND DEPENDENCE** section to include detailed information about abuse and dependence.
- Modification to (or addition of) **OVERDOSAGE** section.
- Addition of the following subsections to the **PATIENT COUNSELING INFORMATION** section:
  - Addiction, Abuse, and Misuse
  - Life-threatening Respiratory Depression
  - Accidental Ingestion
  - Interactions with Alcohol and Other CNS Depressants
  - Serotonin Syndrome
  - Adrenal Insufficiency
  - Pregnancy; *Neonatal Opioid Withdrawal Syndrome, Embryo-Fetal Toxicity*

- Lactation
- Disposal of Unused [TRADENAME]
- Addition of a **MEDICATION GUIDE**

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 attached labeling template, 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.

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 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) – (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.”

### **UPDATE LABELING**

Your prescribing information (PI) approved in “old” format must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(e\)](#) and [201.80](#).

Include the following documents in your application to facilitate review:

- “Track changes” WORD version of your proposed PI that tracks only the addition of the required safety labeling language and the deletion of approved labeling that results from the addition of the required safety labeling language. All approved labeling must be accounted for in the proposed labeling, i.e., it must either be retained or deleted using “track changes”.
- “Clean” version of the last approved PI
- “Clean” version of the proposed PI

The PI must contain a summary of the essential scientific information needed for the safe and effective use of your product and must be informative and accurate and neither promotional in tone nor false or misleading. You must update your PI when new information becomes available that causes the labeling to become inaccurate, false, or misleading [see [21 CFR 201.56\(a\)](#)].

The attached template represents updated class labeling for all IR opioid analgesic products. We request that you adopt the attached IR opioid class template labeling, so as to furnish adequate information for the safe and effective use of [TRADENAME]. Some of this information may currently be in labeling; however, we request that you use this template language and formatting to align the labeling of IR opioid analgesic products.

As directed by the template, certain sections of labeling will include product-specific information that is part of approved labeling. Our expectation is that only currently approved product-specific information would be included in proposed labeling.

### **VOLUNTARY PLR CONVERSION**

We request that you submit draft labeling that adopts the template language in a separate prior approval supplement no later than 60 days from the date of this letter. Although your labeling is not required to be converted to PLR format, we strongly encourage that, instead of proposing revisions in “old” format labeling, you address these updates in PLR-converted labeling (using pertinent aspects of the attached labeling as a template) because “old” formatted labeling may not effectively communicate the updated information.

Clearly mark on the cover letter “**Labeling/PLR Conversion**” and include the following documents in your application to facilitate its review:

- “Track Changes” WORD version of your proposed PI that tracks the addition of both proposed safety labeling changes (as submitted with the Safety Labeling Change supplement described above) and the addition of template language. Also track the deletion of approved labeling that results from the addition of the proposed safety labeling language and the adoption of the template. All approved labeling must be accounted for in the proposed labeling, i.e., it must either be retained or deleted using “track changes”.
- Annotated labeling, in table format, with a left column showing the approved language and a right column showing the disposition of that approved language, i.e., whether the language was deleted or relocated (and stating where it was moved), in the newly proposed PLR-formatted labeling. The entire approved label must be accounted for in this annotated labeling.
- “Clean” version of the last approved PI in “old” format
- “Clean” version of the proposed PI in PLR format

FDA believes that the provided labeling template reflects the most recent understanding of the class effects of immediate-release opioids. If you disagree with a particular aspect of the labeling language, indicate your rationale and proposed revisions on your “track changes” and “clean” labeling.

Finally, it is acceptable to combine both supplements described above. However, should you choose to submit a single supplement addressing both the Safety Labeling Change requirements, and template adoption requests, you must submit that supplement within 30 days of this letter, in accordance with section 505(o)(4) of the FDCA.

The templates with the proposed labeling changes are attached.

If you have any questions, contact 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