



NDA [#####]

LABELING SUPPLEMENT AND PMR REQUIRED

[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 [TRADE NAME].

Sections 505(o)(3) and 505(o)(4) and of the Federal Food, Drug, and Cosmetic Act (FDCA) authorize FDA to require holders of approved drug and biological product applications, on the basis of new safety information, to conduct postmarketing studies and clinical trials for certain purposes and to make safety-related labeling changes.

In May 2012, a discussion of the efficacy of analgesics in chronic non-cancer pain took place at the National Institutes of Health (NIH) (“NIH workshop”).¹ During the discussion, presenters raised concerns about the safety of opioids at higher doses, including those pertaining to known serious risks of opioid use, such as misuse, abuse, hyperalgesia (which itself can result in the use of higher doses of opioid analgesics),² addiction, overdose, and death. Stakeholders have also raised concerns about the appropriate scope of the indication for opioid analgesics and the possibility of limiting dosage and duration of treatment for these drugs.³

Stakeholder and commenter concerns regarding the safety of high-dose opioid analgesics, and requests made for limits on dosage and duration of opioid analgesic treatment resulted in a review of stakeholder and commenter submissions, as well as additional issue-specific literature reviews, to more fully understand what is known about the serious risks associated with ER/LA opioid analgesics. Based on our review of relevant literature, FDA has concluded that more data are needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics. Thus, FDA is requiring

¹ Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop (*see* <http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm>). Information and comments from that workshop are available at www.regulations.gov, docket number FDA-2012-N-0067.

² *See, e.g.*, Chapman CR, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: the effects of chronic opioid pharmacotherapy on acute pain. *J Pain* 2011;12:1240-6.

³ *See, e.g.*, Physicians for Responsible Opioid Prescribing (PROP) citizen petition, docket number FDA-2012-P-0818.

ER/LA opioid analgesic drug sponsors to conduct post-marketing studies and a clinical trial to assess these risks.

FDA has also become aware of the increasing frequency of neonatal abstinence syndrome (NAS), a term which includes neonatal opioid withdrawal syndrome (NOWS), as well as neonatal withdrawal from other drugs. An assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001).⁴ The same study documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001]). Further, with respect to overdose deaths, a CDC analysis published in February 2013, documents an 11th straight year of increases in drug overdose deaths, with opioids being involved in a large percentage of the pharmaceutical overdose deaths (75.2%), either alone or in combination with other drugs.⁵ FDA has determined that these study findings, in addition to the data and information discussed above, demonstrate the continuing trends of serious risks related to the use of opioid analgesics, and the need for modifications to product labeling to more effectively communicate the serious risks associated with ER/LA⁶ opioid analgesic use overall, and during pregnancy, and to more clearly describe the population in whom these drugs should be used, in light of these serious risks.

FDA's analyses of the medical literature described above and the input of FDA stakeholders and commenters noted above are considered to be "new safety information" as defined in section 505-1(b)(3) of FDCA.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

⁴ Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307 (18): 1934-30.

⁵ Jones CM, Mack, KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA* 2013; 309(7): 657-9.

⁶ ER/LA opioids are the focus of the safety labeling changes because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids. See Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf>). Further, because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid non-opioid combinations. This may make certain ER/LA opioids more desirable in the eyes of opioid abusers and addicts, and it increases the risk of a fatal outcome in the event of an overdose.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which [DRUG] is a member. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.
- b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

- 2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

- 2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

- 2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia³ associated with the class of ER/LA opioids, of which [DRUG] is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial to provide the best information possible.

Submit the protocols to your IND [#####], with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “**Required Postmarketing Protocol Under 505(o)**,” “**Required Postmarketing Final Report Under 505(o)**,” “**Required Postmarketing Correspondence Under 505(o)**.”

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that, to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

SAFETY LABELING CHANGE

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 ER/LA opioid analgesics, of which [TRADENAME] is a member.

Note that the labeling that follows addresses the safety labeling changes only and does not include the full text of product labeling. The cross references may require adjustment in your final product labeling.

HIGHLIGHTS

BOXED WARNING

In the boxed warning in Highlights, include the following text:

- **Tradename exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow Tradename (formulation) whole to avoid exposure to a potentially fatal dose of (active opioid). (5.2)**
- **Accidental consumption of Tradename, especially in children, can result in fatal overdose of (active opioid). (5.2)**
- **For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome. (5.3)**

For products with an interaction with alcohol, also include the following:

- **Instruct patients not to consume alcohol or any products containing alcohol while taking Tradename because co-ingestion can result in fatal plasma (active opioid) levels. (5.4)**

INDICATIONS AND USAGE

Under this heading in Highlights, include the full text from this section of the Full Prescribing Information (plus the required pharmacologic class).

DOSAGE AND ADMINISTRATION

Under this heading in Highlights, include the following:

- For opioid-naïve and opioid non-tolerant patients, initiate with X mg (formulation) orally every X hours. (2.1)

For products for which a conversion table is available, include the following bullet.

- To convert to Tradename from another opioid, use available conversion factors to obtain estimated dose. (2.1)

If specific recommendations on a titration scheme are available, include the following bullet.

- Dose can be increased every X to X days, using increments of X mg every X hours (i.e., X mg per day). (2.2)

WARNINGS AND PRECAUTIONS

Under this heading in Highlights, include the following:

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)

TABLE OF CONTENTS

Update the **TABLE OF CONTENTS** to reflect the changes in the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION

BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL *(last warning only for products that have an interaction with alcohol)*

Addiction, Abuse, and Misuse

Tradename exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Tradename, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Tradename. Monitor for respiratory depression, especially during initiation of Tradename or following a dose increase. Instruct patients to swallow Tradename (formulation; e.g., tablets, capsules) whole; crushing, chewing, or dissolving Tradename (formulation) can cause rapid release and absorption of a potentially fatal dose of (active opioid) *[see Warnings and Precautions (5.2)]*.

Accidental Exposure

Accidental consumption of even one dose of Tradename, especially by children, can result in a fatal overdose of (active opioid) [see Warnings and Precautions (5.2)].

Neonatal Opioid Withdrawal Syndrome

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts [see Warnings and Precautions (5.3)].

Interaction with Alcohol *(This subheading and text should be included in the boxed warning only for products that have an interaction with alcohol.)*

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Tradename. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see Warnings and Precautions (5.4)].

1 INDICATIONS AND USAGE

Tradename is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Tradename for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Tradename is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Tradename should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with Tradename [see Warnings and Precautions (5.2)].

Tradename (formulation) must be taken whole, one (formulation) at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see Patient Counseling

To calculate the estimated Tradename dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral (active opioid) daily dose.
If the product's total daily dose is to be given in divided doses, describe here immediately following the sentence above (e.g., The daily dose should then be divided in half for administration every 12 hours.)
- For patients on a regimen of more than one opioid, calculate the approximate oral (active opioid) dose for each opioid and sum the totals to obtain the approximate total (active opioid) daily dose.
If the product's total daily dose is to be given in divided doses, describe here immediately following the sentence above (e.g., The daily dose should then be divided in half for administration every 12 hours.)
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate Tradename strength(s) available.

Example conversion from a single opioid to Tradename:

Step 1: Sum the total daily dose of the opioid (in this case, *insert name and dosage regimen of example former opioid*)

XX mg former opioid X times daily = XX mg total daily dose of former opioid

Step 2: Calculate the approximate equivalent dose of oral (active opioid) based on the total daily dose of the current opioid using Table 1

XX mg total daily dose of former opioid x Conversion Factor = XX mg of oral (active opioid) daily

Step 3: Calculate the approximate starting dose of Tradename to be given every X hours.

Round down, if necessary, to the appropriate Tradename (formulation) strengths available.

XX mg Tradename every X hours

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to Tradename.

For products that do not have conversion tables, include instructions for conversion from other opioids or if all patients are to be titrated from the lowest dose when switched to this product.

Conversion from Methadone to Tradename

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

If any other product-specific conversion instructions are available, insert them here.

2.2 Titration and Maintenance of Therapy

Individually titrate Tradename to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Tradename to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

If specific recommendations on a titration scheme are available, insert here (e.g., Increase the dose of Tradename every X to X days as needed to achieve adequate analgesia, using increments of X mg every X hours.)

Patients who experience breakthrough pain may require a dose increase of Tradename, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the Tradename dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse (Replaces subsection “Abuse Potential”)

Tradename contains (active opioid), a Schedule II controlled substance. As an opioid, Tradename exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence (9)*]. As modified-release products such as Tradename deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of (active opioid) present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Tradename and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

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 or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of Tradename for the proper management of pain in any given patient. Patients at increased risk may be prescribed

modified-release opioid formulations 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.

Abuse or misuse of Tradename by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the (active opioid) and can result in overdose and death [*see Overdosage (10)*].

5.2 Life-threatening Respiratory Depression (Now incorporates subsection “Accidental Exposure”)

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [*see Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Tradename, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with Tradename and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of Tradename are essential [*see Dosage and Administration (2)*]. Overestimating the Tradename dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental consumption of even one dose of Tradename, especially by children, can result in respiratory depression and death due to an overdose of (active opioid).

5.3 Neonatal Opioid Withdrawal Syndrome (New)

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and requires management according to protocols developed by neonatology experts.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants (Replaces subsections “Interactions with CNS Depressants and Illicit Drugs” and “Interactions with Alcohol”)

Include this paragraph only for products that have an interaction with alcohol.

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on Tradename therapy. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see *Clinical Pharmacology (12.3)*].

Hypotension, profound sedation, coma, respiratory depression, and death may result if Tradename is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of Tradename in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin Tradename is made, start with Tradename X mg every X hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [see *Drug Interactions (7.x)*].

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Tradename and when Tradename is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

7.1 Alcohol (*Include this subsection for products with an interaction with alcohol.*)

Concomitant use of alcohol with Tradename can result in an increase of (active opioid) plasma levels and potentially fatal overdose of (active opioid). Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on Tradename therapy [see *Clinical Pharmacology (12.3)*].

7.X CNS Depressants

The concomitant use of Tradename with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and Tradename for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [see *Dosage and Administration (2.2) and Warnings and Precautions (5.4)*].

7.X Drugs Affecting Cytochrome P450 Isoenzymes (*Include subsection only for products that have an effect on cytochrome P450 isoenzymes*)

Inhibitors of CYP3A4 and 2D6

Because the CYP3A4 isoenzyme plays a major role in the metabolism of (active opioid), drugs that inhibit CYP3A4 activity may cause decreased clearance of (active opioid) which could lead to an increase in (active opioid) plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP 2D6 and 3A4 inhibitors. If co-administration with Tradename is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of (active opioid) and, therefore, may cause increased clearance of the drug which could lead to a decrease in (active opioid) plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to (active opioid). If co-administration with Tradename is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [*see Warnings and Precautions (5.3)*].

Teratogenic Effects - Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Tradename should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Follow with drug-specific nonclinical data.

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of Tradename, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death [*see Warnings and Precautions (5.1)*]. Instruct patients not to share Tradename with others and to take steps to protect Tradename from theft or misuse.

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 dose is increased, and that it can

occur even at recommended doses [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Consumption

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store Tradename securely and to dispose of unused Tradename by flushing the (formulation) down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that chronic use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening [see *Warnings and Precautions (5.3)*].

Interactions with Alcohol and other CNS Depressants

For products with an interaction with alcohol, include the following as the first paragraph under this subheading:

Instruct patients not to consume alcoholic beverages, as well as prescription and over-the counter products that contain alcohol, during treatment with Tradename. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see *Warnings and Precautions (5.4)*].

Inform patients that potentially serious additive effects may occur if Tradename is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

MEDICATION GUIDE

In addition to the changes described above, the new safety information should be included in the medication guide for the class of ER/LA opioid analgesics, of which Tradename is a member. Amend the following updated medication guide with appropriate product-specific information:

Medication Guide

TRADENAME (phonetic pronunciation) (drug substance) Drug formulation, CII

TRADENAME is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about TRADENAME:

- **Get emergency help 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.

- Never give anyone your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

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

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** TRADENAME may harm your unborn baby. Long-term (chronic) use during pregnancy can cause life-threatening withdrawal symptoms in your newborn baby.
- **breastfeeding.** TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TRADENAME with certain other medicines can cause serious side effects.

When taking TRADENAME:

- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take your prescribed dose every x hours, at the same time every day. Do not take more than your prescribed dose in x hours. If you miss a dose, take your next dose at your usual time the next day.
- Do not cut, break, chew, crush, dissolve, snort, or inject TRADENAME because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TRADENAME without talking to your healthcare provider.**
- After you stop taking TRADENAME, flush any unused tablets down the toilet.

While taking TRADENAME DO NOT:

- Drive or operate heavy machinery until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with TRADENAME may cause you to overdose and die.

The possible side effects of TRADENAME are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, low blood pressure when changing positions, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

**This Medication Guide has been approved by the U.S. Food and Drug Administration
Issue: Month 2013**

Your revised Medication Guide will be considered part of the proposed REMS described below.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval 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. 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.**”

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

Furthermore, we request that you make additional revisions to other sections of the product labeling, as described below, 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 provide it in this format in an effort to align the labeling of the ER/LA opioid analgesic products.

Add to the end of the **WARNINGS AND PRECAUTIONS** subsection entitled “**Addiction, Abuse, and Misuse**”:

Opioid agonists such as Tradename are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Tradename. Strategies to reduce these risks include prescribing the drug in the

smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

For products that have a subsection in **DRUG INTERACTIONS** called “**Interactions with Mixed Agonist/Antagonist Opioid Analgesics**”, replace the text with the following revised paragraph:

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) may reduce the analgesic effect of Tradename or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist analgesics in patients receiving Tradename.

Replace the **USE IN SPECIFIC POPULATIONS** subsection “**Labor and Delivery**” with the following revised paragraph:

Opioids cross the placenta and may produce respiratory depression in neonates. Tradename is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

Following the approval of the safety labeling changes, a REMS modification will be required to incorporate the approved safety labeling changes into the REMS materials, as applicable.

If you have any questions, call [PROJECT MANAGER NAME], Senior Regulatory Health Project Manager, at (301) 796-[#####].

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research