DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs 075045 (1 mg/mL, 1mL vial; 2 mg/mL, 1mL and 2mL vial)
075046 (2 mg/mL, 10 mL vial)

LABELING ORDER

West-Ward Pharmaceuticals Corp.
U.S. Agent for West-Ward Pharmaceuticals International Limited
2 Esterbrook Lane
Cherry Hill, NJ 08003

Attention: J. Barton Kalis
Sr. Director, Regulatory Affairs

Dear Mr. Barton:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Butorphanol Tartrate Injection USP, 1 mg/mL, 1 mL vial; 2 mg/mL, 1 mL, 2 mL and 10 mL vial.

On March 22, 2016, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of opioid products to address the risks of misuse/abuse/addition/overdose/death, neonatal opioid withdrawal syndrome, serotonin syndrome, adrenal insufficiency, and androgen deficiency. On August 31, 2016, we also sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of opioid products to to address the increased risk of overdose death with concomitant use of opioid analgesics and benzodiazepines. The decision to require safety labeling changes was based on new safety information about these risks identified since these products were approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

Further reference is made to the emails sent by Hyon J. Kim on November 18, 2016, notifying you of the final labeling template which was attached and on November 21, 2016 as a final reminder to submit in response to the Safety Labeling Change Notification Letters. You were also advised that requirements under section 505(o)(4) of the Act apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your products, because your applications have not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

As of the date of this letter, the Agency has received no correspondence from you.

Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the March 22, 2016 and August 31, 2016 letters, and November 18, 2016 and November 20, 2016 emails (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the March 22, 2016 and August 31, 2016 letters must be received by FDA by December 31, 2016, for Butorphanol Tartrate Injection USP, 1 mg/mL, 1 mL vial; 2 mg/mL, 1 mL, 2 mL and 10 mL vial.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by December 21, 2016, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf. The appeal should be submitted as a correspondence to your ANDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 22, Room 6486
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Hyon J. Kim
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3625A
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Khushboo Sharma, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. Appeals received by the Agency later than December 21, 2016, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your products to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your products and injunction.

If you have any questions, contact Hyon J. Kim, Labeling Project Manager, at (240) 402-7766 or Hyon.Kim@fda.hhs.gov.

Sincerely,

Kathleen Uhl, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Safety Labeling Change Notification Letters
Email with Final Labeling Template

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs: See attached list

SAFETY LABELING CHANGE NOTIFICATION

PAREXEL International
U.S. Agent for Bedford Laboratories
4600 East-West Highway
Suite 350
Bethesda, MD 20814

Attention: Beth Ferguson
Director

Dear Ms. Ferguson:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) listed in the attachment.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved new drug applications (NDAs) and biological license applications (BLAs) to make safety related labeling changes based upon "new safety information," as defined in section 505-1(b)(3) of the FDCA, about which FDA becomes aware after approval of the drug or biological product. 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.

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 Butorphanol Tartrate Injection, USP was originally approved, we have become aware of two recent publications that provide evidence of persistent abuse and overdose mortality associated with IR opioid products.[1,2] An additional study documented cases of neonatal

abstinence syndrome[3] (NAS) occurring in infants born to mothers who were dispensed IR opioid products during pregnancy.[4]

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.[5] 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.[6]

SEROTONIN SYNDROME WITH CONCOMITANT USE OF SEROTONERGIC DRUGS

Since Butorphanol Tartrate Injection, USP was originally approved, we have become aware of publications[7,8] 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.

ADRENAL INSUFFICIENCY

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[1] 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.

[2] 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.

[3] The term "neonatal abstinence syndrome" is a term used frequently in the medical literature that encompasses "neonatal opioid withdrawal syndrome" as well neonatal withdrawal from other drugs (e.g., benzodiazepines, selective serotonin reuptake inhibitors).

[4] Patrick SW, Dudley, J, Martin PR et al. (2015) Prescription opioid epidemic and infant outcomes. Pediatrics, 135 (5): 842-850.

[5] 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.

[6] See section 505-1(b)(3) of the FD&C Act.

[7] Rastogi R, Swarm RA, Patel TA. Case Scenario: Opioid Association with Serotonin Syndrome. Anesthesiology 2011; 115(6): 1291-8.

[8] Altman CS, Jahangiri MF. Serotonin Syndrome in the Perioperative Period. Anesthesia and Analgesia 2010; 110(2): 526-8.

Since Butorphanol Tartrate Injection, USP was originally approved, we have become aware of publications[9,10] 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 Butorphanol Tartrate Injection, USP was originally approved, we have become aware of publications in the medical literature describing androgen deficiency in patients with long-term exposure to opioids.[11,12] 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.[13,14]

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 information appended to this letter should be included in the labeling for the class of IR opioid products, of which Butorphanol Tartrate Injection, USP is a member.

Note that the appended information includes the required safety labeling changes only and does not reflect the full text of product labeling. Generally, the revised text shown below should replace any existing labeling language on that topic in your current labeling. The cross references may require adjustment in your final product labeling.

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,

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[9] Debono M, Chan S, Rolfe C, et al. Tramadol-induced adrenal insufficiency. Eur J Clin Pharmacol 2011; 67:865–7.
[10] Oltmanns KM et al. Chronic fentanyl application induces adrenocortical insufficiency. Journal of Internal Medicine 2005;257:478–80.
[11] 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.
[12] Daniell HW. Opioid endocrinopathy in women prescribed sustained-action opioids for control of nonmalignant pain. J of Pain 2008; 9:28-36.
[13] Kalra PS, et al. Opiate-induced hypersensitivity to testosterone feedback: pituitary involvement. Endocrinology 1988; 122:997-1003, 1988.
[14] Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain 2009; 25:170-175.

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). Your supplement should only include proposed changes made in accordance with the appended direction. Any other proposed labeling changes should be submitted in a separate supplement and should not be identified as a safety labeling change.

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.

Failure to submit a response within 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A), misbranding charges under section 502(z), and an order under 505(o)(4) 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 have any questions, contact Carol Yun, Labeling Project Manager, at (240) 402- 6244 or carol.yun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Attached:
List of Affected ANDAs
Required Safety Labeling Change Language

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL A HOLQUIST
03/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDAs 075045 (1 mg/mL, 1mL vial; 2 mg/mL, 1mL and 2mL vial)
075046 (2 mg/mL, 10 mL vial)

SAFETY LABELING CHANGE NOTIFICATION

West-Ward Pharmaceuticals Corp.
U.S. Agent for Eurohealth International Sàrl
2 Esterbrook Lane
Cherry Hill, NJ 08003

Attention: J. Barton Kalis
Director, Regulatory Affairs

Dear Mr. Kalis:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Butorphanol Tartrate Injection USP, 1 mg/mL, 1 mL vial; 2 mg/mL, 1 mL, 2 mL and 10 mL vial.

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved new drug applications (NDAs) and biological license applications (BLAs) to make safety related labeling changes based upon "new safety information," as defined in section 505-1(b)(3) of the FDCA, about which FDA becomes aware after approval of the drug or biological product. 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.

Since Butorphanol Tartrate Injection, USP, was originally approved, 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

[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.

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 (please be sure to replace all instances of "[TRADENAME]" with appropriate product specific information):

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
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, PRECAUTIONS; Drug Interactions].*

- **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.**

WARNINGS
[The following subsection should replace **(Risks due to) Interactions with Central Nervous System Depressants.**]

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 PRECAUTIONS; Drug Interactions]*.

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 PRECAUTIONS; Drug Interactions)* and *PRECAUTIONS; Information for Patients].*

PRECAUTIONS

Information for Patients

[The following subsection should replace Interactions with Alcohol and Other 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; Drug Interactions].*

Drug Interactions

[The following subsection should replace (Interaction with) Central Nervous System Depressants.]

Benzodiazepines and other Central Nervous System (CNS) Depressants
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increases the risk of respiratory depression, profound sedation, coma, and death.

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 *WARNINGS*].

MEDICATION GUIDE

[Under **Important information about [TRADENAME]**, add a bullet in the second position as follows]

- 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 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). Your supplement should only include proposed changes made in accordance with the above direction. Any other proposed labeling changes should be submitted in a separate supplement and should not be identified as a safety labeling change.

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.

Failure to submit a response within 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A), misbranding charges under section 502(z), and an order under 505(o)(4) 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

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, contact Kyle Snyder, Labeling Project Manager, at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

Sincerely,

{see appended signature page}

John R. Peters, M.D.
Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R PETERS
08/31/2016