DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs 070765, 070766, and 070683

LABELING ORDER

Frontida Biopharm Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Rovinsky
Director, Regulatory Compliance and Risk Management

Dear Mr. Rovinsky:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Chlordiazepoxide and Amitriptyline Hydrochloride Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg, and Oxazepam Tablets USP, 15 mg.

On August 31, 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 benzodiazepines regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of benzodiazepines and opioids. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was 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 voicemail left by the Carol Lee on October 13, 2016 to Robert Rovinsky stating that you must submit a response to the August 31, 2016 Notification Letter. 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and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.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 August 31, 2016, letter (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 August 31, 2016, letter must be received by FDA

by December 31, 2016, for Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP and Oxazepam Tablets, USP.

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:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
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:

Carol Lee
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
Bldg. 75, Room 3631
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 Amy Bertha, 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 product 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 product and injunction.

If you have any questions, contact Carol Lee, Labeling Project Manager, at (240) 402-6244 or carol.lee@fda.hhs.gov.

Sincerely,

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

ENCLOSURE: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDAs 070765 (5 mg/12.5 mg)
070766 (10 mg/25 mg)

SAFETY LABELING CHANGE NOTIFICATION

Frontida Biopharm Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Rovinsky
Director, Regulatory Compliance and Risk Management

Dear Mr. Rovinsky:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Chlordiazepoxide and Amitriptyline Hydrochloride Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg.

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 Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP, was originally approved, we have become aware of information derived from peer-reviewed publications[1,2,3,4] that should be included in the labeling of benzodiazepines regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of benzodiazepines and opioids.

We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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[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] 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.

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 benzodiazepines as follows:

Boxed Warning (Insert before DESCRIPTION and include in existing Boxed Warning before Suicidality and Antidepressant Drugs)

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings, Drug-Drug Interactions]*.

- 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 for signs and symptoms of respiratory depression and sedation.

Warnings (Insert at beginning of Warnings Section):

Risks from Concomitant Use with Opioids: Concomitant use of benzodiazepines, including chlordiazepoxide and amitriptyline, and opioids may result in profound sedation, respiratory depression, coma, and death. 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 opioids alone. If a decision is made to prescribe chlordiazepoxide and amitriptyline concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of chlordiazepoxide and amitriptyline than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking chlordiazepoxide and amitriptyline, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when chlordiazepoxide and amitriptyline is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined. [see Drug Interactions].

Drug Interactions (insert at the beginning of the Drug-Drug Interactions section):

> The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Medication Guide: See appended new Medication Guide for dispensing with chlordiazepoxide and amitriptyline.

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. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. 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 Carol Lee, Labeling Project Manager, at (240) 402-6244 or carol.lee@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

Enclosure:
Medication Guide Template

MEDICATION GUIDE

Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, C-IV

[KLOR-dye-AZ-e-POX-ide/A-mi-TRIP-ti-leen]

What is the most important information I should know about chlordiazepoxide and amitriptyline hydrochloride?

- **This medicine contains chlordiazepoxide. Chlordiazepoxide is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- **Suicidal thoughts or actions.** Chlordiazepoxide and amitriptyline hydrochloride and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults (18 to 24 years of age) **within the first few months of treatment or when the dose is changed.**
- **Depression or other serious mental illnesses are the most important cause of suicidal thoughts of actions.**
- **How can I watch for and try to prevent suicidal thoughts and actions?**
  - Pay particular attention to such changes when chlordiazepoxide and amitriptyline hydrochloride is started or when the dose is changed.
  - Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.
  - **Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:**
    - attempts to commit suicide
    - acting on dangerous impulses
    - acting aggressive or violent
    - thoughts about suicide or dying
    - new or worse depression
    - new or worse anxiety or panic attacks
    - feeling agitated, restless, angry or irritable
    - trouble sleeping (insomnia)
    - an increase in activity or talking more than what is normal for you (mania)
    - other unusual changes in behavior or mood
- **Chlordiazepoxide and amitriptyline hydrochloride can make you sleepy or dizzy, and can slow your thinking and motor skills.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how chlordiazepoxide and amitriptyline hydrochloride affects you.
  - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking chlordiazepoxide and amitriptyline hydrochloride without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, chlordiazepoxide and amitriptyline hydrochloride may make your sleepiness or dizziness much worse.
- Do not take more chlordiazepoxide and amitriptyline hydrochloride than prescribed.

What is chlordiazepoxide and amitriptyline hydrochloride?

- Chlordiazepoxide and amitriptyline hydrochloride is a prescription medicine used to treat moderate to severe depression that can happen with moderate to severe anxiety.
- **Chlordiazepoxide and amitriptyline hydrochloride is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep chlordiazepoxide and amitriptyline hydrochloride in a safe place to prevent misuse and abuse. Selling or giving away chlordiazepoxide and amitriptyline hydrochloride may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if chlordiazepoxide and amitriptyline hydrochloride is safe and effective in children.

Do not take chlordiazepoxide and amitriptyline hydrochloride if you:

- are allergic to benzodiazepines or tricyclic antidepressant medicines
- take a medicine called a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
- are recovering from a heart attack (myocardial infarction)

Before you take chlordiazepoxide and amitriptyline hydrochloride, tell your healthcare provider about all of your medical conditions, including if you:

- have bipolar disorder (manic depression) or mania
- have a history of drug or alcohol abuse or addiction
- have eye problems
- have problems urinating or emptying your bladder
- have kidney or liver problems
- have or had heart problems, including heart attack or a stroke
- have or have had seizures

- have a thyroid problem
- plan to have surgery
- receive electroconvulsive therapy (ECT)
- are pregnant or plan to become pregnant. Chlordiazepoxide may harm your unborn baby. Avoid taking chlordiazepoxide and amitriptyline hydrochloride during the first trimester of pregnancy. Tell your healthcare provider right away if you become pregnant during treatment with chlordiazepoxide and amitriptyline hydrochloride.
- are breastfeeding or plan to breastfeed. It is not known if chlordiazepoxide and amitriptyline hydrochloride passes into your breast milk. You should not breastfeed while taking chlordiazepoxide and amitriptyline hydrochloride. Talk to your healthcare provider about the best way to feed our baby if you take chlordiazepoxide and amitriptyline hydrochloride.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking chlordiazepoxide and amitriptyline hydrochloride with certain other medicines can cause side effects or affect how well chlordiazepoxide and amitriptyline hydrochloride or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take chlordiazepoxide and amitriptyline hydrochloride?

- Take chlordiazepoxide and amitriptyline hydrochloride exactly as your healthcare provider tells you to take it.
- If you take too much chlordiazepoxide and amitriptyline hydrochloride, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of chlordiazepoxide and amitriptyline hydrochloride?
Chlordiazepoxide and amitriptyline hydrochloride may cause serious side effects, including:

- **See "What is the most important information I should know about chlordiazepoxide and amitriptyline hydrochloride?"**
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking chlordiazepoxide and amitriptyline hydrochloride suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping chlordiazepoxide and amitriptyline hydrochloride to avoid withdrawal symptoms.
- **Abuse and dependence.** Taking chlordiazepoxide and amitriptyline hydrochloride can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.

The most common side effects of chlordiazepoxide and amitriptyline hydrochloride include:

- drowsiness
- dry mouth
- constipation
- blurred vision
- dizziness
- bloating

These are not all the possible side effects of chlordiazepoxide and amitriptyline hydrochloride. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store chlordiazepoxide and amitriptyline hydrochloride?

- Store at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep chlordiazepoxide and amitriptyline hydrochloride in a tightly closed, child-resistant container and out of the light.
- **Keep chlordiazepoxide and amitriptyline hydrochloride and all medicines out of the reach of children.**

General information about the safe and effective use of chlordiazepoxide and amitriptyline hydrochloride.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use chlordiazepoxide and amitriptyline hydrochloride for a condition for which it was not prescribed. Do not give chlordiazepoxide and amitriptyline hydrochloride to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about chlordiazepoxide and amitriptyline hydrochloride that is written for health professionals.

What are the ingredients in chlordiazepoxide and amitriptyline hydrochloride tablets?

Active ingredient: chlordiazepoxide, amitriptyline (as the hydrochloride salt)

Inactive ingredients: [As applicable to proposed product]

Manufactured by: xxxxxxxxxxxxxxxxxxxxxxx.

For more information, go to www.XXXX.com or call 1-XXX-XXX-XXXX.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: Month/Year

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

Reference ID: 4029523

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 070683

SAFETY LABELING CHANGE NOTIFICATION

Frontida Biopharm Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Attention: Robert Rovinsky
Director, Regulatory Compliance and Risk Management

Dear Mr. Rovinsky:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oxazepam Tablets USP, 15 mg.

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 Oxazepam Tablets, USP, was originally approved, we have become aware of information derived from peer-reviewed publications[1,2,3,4] that should be included in the labeling of benzodiazepines regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of benzodiazepines and opioids.

We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

[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] 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.

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 new safety information should be included in the labeling for benzodiazepines as follows:

Boxed Warning (Insert before DESCRIPTION):

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings, Drug Interactions]*.

- 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 for signs and symptoms of respiratory depression and sedation.

Warnings (Insert at beginning of Warnings Section):

Risks from Concomitant Use with Opioids: Concomitant use of benzodiazepines, including oxazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. 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 opioids alone. If a decision is made to prescribe oxazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of oxazepam than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking oxazepam, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when oxazepam is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined. [see Drug Interactions].

In **PRECAUTIONS**, add the subsection **Drug Interactions** directly after the subsection **Information for Patients:**

Drug Interactions:

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids

interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Medication Guide: See appended new Medication Guide for dispensing with oxazepam.

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. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. 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 Carol Lee, Labeling Project Manager, at (240) 402-6244 or carol.lee@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

Enclosure:
Medication Guide Template

MEDICATION GUIDE

Oxazepam (ox-AZE-e-pam) Tablets, C-IV

What is the most important information I should know about oxazepam?

- **Oxazepam is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- **Oxazepam can make you sleepy or dizzy, and can slow your thinking and motor skill.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how oxazepam affects you.
  - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking oxazepam without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, oxazepam may make your sleepiness or dizziness much worse.
- Do not take more oxazepam than prescribed.

What is oxazepam?

- Oxazepam is a prescription medicine used:
  - to treat anxiety disorders
  - for the short-term relief of the symptoms of anxiety or anxiety that can happen with depression
  - to treat anxiety, tension, agitation and irritability in elderly people
  - to relieve the symptoms of alcohol withdrawal including agitation, shakiness (tremor), anxiety associated with acute alcohol withdrawal.
- **Oxazepam is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep oxazepam in a safe place to prevent misuse and abuse. Selling or giving away oxazepam may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if oxazepam is safe and effective in children under 6 years of age.
- It is known if oxazepam is safe and effective for use longer than 4 months.

Do not take oxazepam if you:

- are allergic to oxazepam or any of the ingredients in oxazepam. See the end of this Medication Guide for a complete list of ingredients in oxazepam.

Before you take oxazepam, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have or have had problems with fainting or low blood pressure
- are pregnant or plan to become pregnant. Oxazepam may harm your unborn baby. You and your healthcare provider should decide if you should take oxazepam while you are pregnant.
- are breastfeeding or plan to breastfeed. Oxazepam may pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take oxazepam.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking oxazepam with certain other medicines can cause side effects or affect how well oxazepam or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take oxazepam?

- See **"What is the most important information I should know about oxazepam?"**
- Take oxazepam exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much oxazepam to take and when to take it.
- If you take too much oxazepam, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking oxazepam?

- Oxazepam can cause you to be drowsy. Do not drive a car, operate heavy machinery, or do other dangerous activity until you know how oxazepam affects you.
- You should not drink alcohol while taking oxazepam. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of oxazepam?

Oxazepam may cause serious side effects, including:

- **See "What is the most important information I should know about oxazepam?"**
- **Low blood pressure.** Oxazepam can cause low blood pressure especially in elderly people.
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking oxazepam suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping oxazepam to avoid withdrawal symptoms.
- **Abuse and dependence.** Taking oxazepam can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.

The most common side effects of oxazepam include:

- drowsiness
- dizziness
- vertigo (sensation of loss of balance)
- headache

These are not all the possible side effects of oxazepam. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store oxazepam?

- Store oxazepam at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep oxazepam in a tightly closed container and out of the light.
- **Keep oxazepam and all medicines out of the reach of children.**

General information about the safe and effective use of oxazepam.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use oxazepam for a condition for which it was not prescribed. Do not give oxazepam to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about oxazepam that is written for health professionals.

What are the ingredients in oxazepam?

Active ingredient: oxazepam

Inactive ingredients: [As applicable to proposed product]

Manufactured by: XXXXXXXXXXXXXXXX

For more information, go to www.XXXX.com or call 1-XXX-XXX-XXXX.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: DATE

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/s/

JOHN R PETERS
08/31/2016

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/s/

CAROL N YUN
12/16/2016
entered on behalf of Kathleen Uhl (see page 3 for signature)