DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDAs 070444 (15 mg)
070445 (30 mg)

LABELING ORDER

Par Pharmaceutical Inc.
One Ram Ridge Rd
Chestnut Ridge, NY 10977

Attention: Robin Heit
Manager, Regulatory Affairs

Dear Ms. Heit:

Please refer to your Abbreviated New Drug Applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Flurazepam Hydrochloride Capsules USP, 15 mg and 30 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 the 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 emails from Carol Lee to Krista Richardson dated October 4, 2016, and October 6, 2016, advising that you must either formally withdraw your applications or maintain up-to-date labeling. 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and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.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 Flurazepam Hydrochloride Capsule, 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 070444 (15 mg)
070445 (30 mg)

SAFETY LABELING CHANGE NOTIFICATION

Par Pharmaceutical Inc.
1 Ram Ridge Road
Chestnut Ridge, NY 10977

Attention: Robin Heit
Manager, Regulatory Affairs

Dear Ms. Heit:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Flurazepam Hydrochloride Capsule USP, 15 mg and 30 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 Flurazepam Hydrochloride Capsule, 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 the concomitant use of benzodiazepines and opioids.

[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.

Reference ID: 4029892

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 benzodiazepines as follows:

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 and Precautions (5.1), Drug Interactions (7.X)]*.

- 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.

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including flurazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids 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 flurazepam 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. Advise both patients and caregivers about the risks of respiratory depression and sedation when flurazepam is used with opioids [see Drug Interactions (7), Patient Counseling Information (17)].

7.X 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 follow patients closely for respiratory depression and sedation.

Reference ID: 4029892

17 Patient Counseling Information

Inform patients and caregivers that potentially fatal additive effects may occur if flurazepam is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider [see Warnings and Precautions (5.1), Drug Interactions (7)].

See attached for the Medication Guide, which includes revisions related to the new safety information described above.

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)."

Reference ID: 4029892

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

Reference ID: 4029892

MEDICATION GUIDE

Flurazepam Hydrochloride Capsules (flur-AZE-e-pam HYE-droe-KLOR-ide), C-IV

What is the most important information I should know about flurazepam hydrochloride?

- **Flurazepam hydrochloride 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.**
- Flurazepam hydrochloride may cause serious side effects that you may not know are happening to you. These side effects include:
  - sleepiness during the day
  - not thinking clearly
  - act strangely, confused, or upset
  - "sleep-walking" or doing other activities when you are asleep like:
    - eating
    - talking
    - having sex
    - driving a car

  Call your healthcare provider right away if you find out that you have done any of the above activities after taking flurazepam hydrochloride.
- Do not take flurazepam hydrochloride unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.
- Do not take more flurazepam hydrochloride than prescribed.

What is flurazepam hydrochloride?

- Flurazepam hydrochloride is a prescription medicine used to treat certain types of insomnia including difficulty falling asleep, waking up often during the night, or waking up early in the morning.
- **Flurazepam hydrochloride is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep in a safe place to prevent misuse and abuse. Selling or giving away flurazepam 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 flurazepam hydrochloride is safe and effective in children.

Do not take flurazepam hydrochloride if you:

- are allergic to flurazepam hydrochloride, other benzodiazepines, or any of the ingredients in flurazepam hydrochloride. See the end of this Medication Guide for a complete list of ingredients in flurazepam hydrochloride. Symptoms of a serious allergic reaction can include:
  - swelling of your face, lips, and throat that may cause difficulty breathing or swallowing
  - nausea and vomiting

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

- have a history of depression, mental illness or, suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- are pregnant or planning to become pregnant. Flurazepam hydrochloride may harm your unborn baby. You and your healthcare provider should decide if you should take flurazepam hydrochloride while you are pregnant.
- are breastfeeding, or plan to breastfeed. Flurazepam hydrochloride may pass through your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take flurazepam hydrochloride.

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

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

Do not take flurazepam hydrochloride with other medicines that can make you sleepy unless your healthcare provider tells you to.

How should I take flurazepam hydrochloride?

- **See "What is the most important information I should know about flurazepam hydrochloride?"**
- Take flurazepam hydrochloride exactly as your healthcare provider tells you to take it.

- Take flurazepam right before you get into bed.
- Do not take flurazepam unless you are able to get a full night's sleep before you must be active again.
- If you take too much flurazepam hydrochloride, get emergency treatment right away.

What should I avoid while taking flurazepam hydrochloride?

- You may still feel drowsy the next day after taking flurazepam hydrochloride. Do not drive, operate machinery, do other dangerous activities or do anything that needs you to be alert until you know how flurazepam hydrochloride affects you.
- You should not drink alcohol while you are taking flurazepam hydrochloride.

What are the possible side effects of flurazepam hydrochloride?

Flurazepam hydrochloride may cause serious side effects, including:

- **See "What is the most important information I should know about flurazepam hydrochloride?"**
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking flurazepam 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 flurazepam hydrochloride to avoid withdrawal symptoms.
- **Other conditions.** Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- **Severe allergic reactions.** Symptoms include swelling of the tongue or throat, and trouble breathing. Other symptoms may include nausea and vomiting. Get emergency medical help right away if you have these symptoms after taking flurazepam hydrochloride.
- **Abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts.
- **Depression.** Pre-existing depression may emerge or worsen during use of benzodiazepines including flurazepam hydrochloride.
- **Abuse and dependence.** Taking flurazepam 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 flurazepam hydrochloride include:

- dizziness
- light-headedness
- loss of coordination
- drowsiness
- staggering
- falling

These are not all the possible side effects of flurazepam 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 flurazepam hydrochloride?

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

General information about the safe and effective use of flurazepam hydrochloride.

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

What are the ingredients in flurazepam hydrochloride?

Active Ingredient: flurazepam hydrochloride

Inactive Ingredients: [As applicable to proposed product]

Manufactured by XXXXXXXXXXXXXXX

If you would like more information, call XXXXXXXXXXXX at X-XXX-XXX-XXXX or visit www.XXXX.com.

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

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

/s/

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