

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022549Orig1s000**

**OTHER ACTION LETTERS**



NDA 022549

**COMPLETE RESPONSE**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) dated and received on December 11, 2009, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) inhalation powder 5 mg and 10 mg.

We acknowledge receipt of your amendments dated August 4, 2011, October 25, 2011 (2), January 10, 2012, January 12, 2012, January 17, 2012, February 1, 2012, February 6, 2012, February 22, 2012, March 8, 2012 (2), March 27, 2012, April 3, 2012, and April 5, 2012.

The August 4, 2011, submission constituted a complete response to our October 8, 2010, action letter.

We also acknowledge receipt of your amendment, received on April 6, 2012, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**FACILITY INSPECTIONS**

During a recent inspection of the Mountain View, CA manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**LABELING**

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format

as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated January 6, 2012, received on January 10, 2012, and amended on February 22, 2012 and March 27, 2012, which contains elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for Adasuve (loxapine) inhalation powder, if it is approved, to ensure that the benefits of the drug outweigh the risk of bronchospasm. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

### **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Labeling

30 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)  
immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
05/02/2012



NDA 022549

**COMPLETE RESPONSE**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your New Drug Application (NDA) dated and received on December 11, 2009 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (Loxapine) Inhalation Powder 5 mg and 10 mg.

We acknowledge receipt of your amendments dated:

February 1, 2010	February 3, 2010	February 4, 2010
February 8, 2010	March 10, 2010	April 6, 2010
April 27, 2010	May 4, 2010	May 20, 2010
June 7, 2010	June 23, 2010	July 1, 2010 (2)
July 15, 2010	July 19, 2010	July 29, 2010
August 18, 2010	August 31, 2010	

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**Clinical**

**Pulmonary Toxicity**

The primary clinical safety concern is the pulmonary toxicity associated with the use of loxapine inhalation powder. Clearly, the toxicity is drug-related. However, an additional component of the toxicity appears to be related to use of the device itself, as demonstrated by the responses in the placebo group. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. To place these findings in perspective, one should note that the standard bronchoprovocation tests cause a decrease in FEV1 of 10-20%. In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV1 of >10%.

Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%. The decreases in FEV1 observed above occurred in the 8 hours after either dosing.

In subjects with asthma or COPD, the FEV1 findings were marked. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Furthermore, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related in the safety studies. Subjects treated with a second dose of loxapine inhalation powder had greater decreases in FEV1 (compared to their first dose), which did not return to baseline at 24 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued from the study before receiving the second dose, due to a decreased FEV1 and/or the need for rescue treatment of respiratory signs and symptoms. As a result, one cannot determine the true nadir of the FEV1 following treatment with loxapine inhalation powder in the pulmonary safety studies.

Additional factors could contribute to an unacceptable risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. As noted above, exposure to loxapine inhalation powder can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease during the episode. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Furthermore, rescue treatment may not be readily available in some settings in which patients would be treated with loxapine inhalation powder. Moreover, sedation from loxapine inhalation powder could obscure respiratory signs and symptoms. Finally, the dosage and administration section of proposed labeling states that loxapine inhalation powder could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1 or respiratory symptoms.

In our opinion, labeling or a risk evaluation and mitigation strategy (REMS) would not provide a reasonable degree of safety regarding the risk of pulmonary toxicity from treatment with loxapine inhalation powder in the intended population. Indeed, it is not clear what approaches might be taken to resolve this important deficiency. Nevertheless, this concern is one that you must attempt to address in your response to this letter.

## Other Issues That Need to be Addressed

### Center for Devices and Radiological Health (CDRH)

1. Based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, a prominent visible flash, and elevated inspired air temperature. These phenomena caused a startle response in some cases, which resulted in incomplete inhalation. Under these conditions, patients unfamiliar with the device may discontinue inhalation and, therefore, not receive the full, intended dose. In fact, it is not clear that the clinical studies (301 and 302) were conducted in patients substantially similar to those for whom this drug might be most useful in the community. It is our impression that the most likely patients to be considered for this product would be patients in an emergency setting in which health care providers may not be familiar with the patients' histories and the patients would not be familiar with this product.

Thus, we request that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting.

You must address the following:

- a. A human factors validation report that includes:
  - i. A detailed analysis of use performance and subjective data;
  - ii. Evaluation and documentation of user performance, use errors and task failures
  - iii. An evaluation of the effectiveness of proposed mitigation strategies (training, device labeling, etc.) through simulated use scenarios;
  - iv. Discussion of how unanticipated failures can be handled; and
  - v. Discussion of any further mitigation strategies necessary and if further validation is necessary.
- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to safe use of the product. The study must evaluate feedback provided by test participants, which focuses on their ability to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
- c. You must conduct a thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients. This analysis should include the independent and integrated aspects of both the device and user interactions. The risk analysis should address whether the device is used in ways that were not anticipated, especially if the device use environment affects device utility and user comprehension. This risk analysis should also include a discussion of the mitigations against use-related risks, and it should evaluate the effectiveness of the mitigations, based on the human factors validation study results.



(b) (4)  
This finding calls into question the suitability of the proposed container closure system.

Appropriate packaging material will need to be selected, and relevant stability data will need to be accumulated and submitted to the application to support an expiry period for the drug product.

3. Data was provided in the application to support the proposed (b) (4) retest period of the heat package. (b) (4)

(b) (4)

4. Data was observed during the preapproval inspection in which at least (b) (4) was observed in the drug film (b) (4)

(b) (4)

5. (b) (4)  
. Provide an explanation for this discrepancy.

6. (b) (4)

7. (b) (4)  
Provide a detailed account as to how you came to this conclusion, bearing in mind that files with the thermogram measurement frame are not stored electronically.

8. Provide full details of the “in-process weight check method that will include measurements from both lid and tray sides of the product” (response 4a to PAI 483 observations).

### **Facility Inspections**

During a recent inspection of the Mountain View, CA manufacturing facility for this application, our field investigator conveyed the deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

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If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

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/s/

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THOMAS P LAUGHREN  
10/08/2010