CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022549Orig1s000

Trade Name: Adasuve

Generic Name: Loxapine inhalation powder

Sponsor: Alexza Pharms

Approval Date: December 21, 2012

Indications: For the acute treatment of agitation associated with schizophrenia or bipolar disorder in adults.

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APPLICATION NUMBER:

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
Rems	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022549

NDA APPROVAL

Alexza Pharmaceuticals, Inc.
Attention: Edwin Kamemoto, Ph.D.
Executive Director, Regulatory Affairs
Alexza Pharmaceuticals, Inc.
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 (FDCA) for Adasuve (loxapine) inhalation powder 10mg.

We acknowledge receipt of your amendments dated June 21, 2012, July 17, 2012, August 20, 2012, September 28, 2012, October 23, 2012, November 8, 2012, November 21, 2012, December 7, 2012, December 13, 2012, and December 19, 2012.

The June 21, 2012, submission constituted a complete response to our May 2, 2012, action letter.

This new drug application provides for the use of Adasuve (loxapine) inhalation powder for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

We acknowledge your June 21, 2012 submission, and your amendment dated December 7, 2012, containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years because necessary studies are highly impractical because there is a very low incidence of bipolar I disorder diagnosed prior to age 10 or schizophrenia diagnosed prior to age 13.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

1891-1 A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. A study to obtain pharmacokinetic data and provide information pertinent to dosing of Adasuve (loxapine) inhalation powder in the relevant population.

Final Protocol Submission Date: May 1, 2013
Study/Trial Completion Date: July 18, 2013
Final Report Submission: January 18, 2014

1891-2 A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to

17 years. A study of the efficacy and safety of Adasuve (loxapine) inhalation powder in the relevant pediatric population.

Final Protocol Submission Date: October 1, 2013
Study/Trial Completion Date: September 30, 2014
Final Report Submission: March 30, 2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess unexpected serious risks of Adasuve (loxapine) due to age-related differences in pharmacokinetics and pharmacodynamics, and a known serious risk of bronchospasm with Adasuve (loxapine).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

1891-3 A single-dose GLP developmental juvenile rat tolerability and toxicokinetic study of loxapine by inhalation route that spans the corresponding ages for the pediatric clinical studies (ages 10 to 17 years). The study will evaluate the potential pharmacodynamic and pharmacokinetic differences among different ages in rats, and the results may apply to potential differences between adults and children.

The timetable you communicated to us on December 5, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: May 31, 2013

1891-4 Conduct a large, non-randomized, open-label, postmarketing observational study to assess the risks of bronchospasm and related respiratory adverse events and serious outcomes (e.g., hospitalization, intubation, mechanical ventilation, or rescue medication for the management of respiratory reactions) associated with Adasuve (loxapine) inhalation powder treatment. The study must have a large sample size (approximately 10,000 patients exposed to Adasuve (loxapine) inhalation powder), in order to adequately characterize the frequency, nature, and severity of the risk of bronchospasm. The study must assess the use of Adasuve

(loxapine) inhalation powder as used in clinical practice under the requirements of the REMS for Adasuve (loxapine) inhalation powder and per the product labeling.

The timetable you communicated to us on December 5, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 1, 2013
Study Completion: June 1, 2015
Final Report Submission: December 1, 2015

Submit the protocol(s) to your IND 73248, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

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

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

<u>POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B</u>

We remind you of your postmarketing commitment:

1891-5 Your agreement to implement, within 6 months of approval, the appropriate controls (routine extraction testing with acceptance criteria) for (b) (4) to ensure that levels remain below the levels that have been qualified by the risk assessments in Module 4.

The timetable you communicated to us on December 5, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2013

Submit clinical protocols to your IND 73248 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, the number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Adasuve (loxapine) powder for inhalation to ensure the benefits of the drug outweigh the risk of bronchospasm.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Pursuant to 505-1(f)(1), we have also determined that Adasuve (loxapine) powder for inhalation can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of bronchospasm that is listed in the labeling. The elements to assure safe use will inform healthcare professionals of the risk of bronchospasm with Adasuve (loxapine); inform healthcare professionals of the safe use of Adasuve (loxapine), including appropriate patient selection, monitoring, and management of bronchospasm; and ensure that patients receive Adasuve (loxapine) in healthcare facilities with on-site resources to manage bronchospasm and/or respiratory failure.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on June 21, 2012, amended on July 25, 2012, September 28, 2012, November 11, 2012, December 7, 2012, and December 19, 2012, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Adasuve (loxapine) powder for inhalation into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

For the current period and cumulatively:

1. The sources of the list of recipients of the Dear Healthcare Professional Letter, the dates of distribution, and the number of letters distributed on each date, the number of undeliverable and returned letters for each distribution date, and for the assessment period.

2. A list of the documents included with each Dear Healthcare Professional Letter distribution, including the revision date(s).

3. Healthcare facility (including the type of facility) and distributor enrollment statistics.

4. The number and type of non-enrolled healthcare facilities that dispensed Adasuve and the number of incidents for each; include a description of the cause and corrective actions taken.

5. The number and summary description of instances where distributors/wholesalers shipped Adasuve to non-enrolled entities; include a description of the cause and corrective actions taken.

6. The number, type, and summary description of instances where distributors/wholesalers denied shipment to healthcare facilities because the facility:

    a. was not enrolled

    b. was dis-enrolled due to non-compliance with the REMS.

    c. had expired enrollment

7. The number and summary description of instances where healthcare settings dispensed Adasuve to outpatients; include a description of the cause and corrective actions taken.

8. The number and percentage of healthcare facilities, by type, that were audited, including:

    a. The number and percentage that lacked training records for relevant staff.

    b. The number and percentage that lacked immediate-access to equipment, medications, and trained personnel to ensure compliance with the REMS safe use conditions.

    c. The number and percentage that lacked documented procedures, protocols, and/or order-sets to ensure compliance with REMS-defined safe use conditions: (1) patient screening prior to treatment with Adasuve, 2) monitoring patients

following treatment with Adasuve, and 3) limiting Adasuve administration to one dose per patient within 24 hours).

9. The number and percentage of healthcare facilities identified in items 8 (a-c) that successfully completed the required corrective and preventive action (CAPA) plan within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.

10. The number and percentage of Wholesaler/Distributors that were audited to ensure that Adasuve is distributed in accordance with the program requirements. For those audited:

    a. The number and percentage that lacked documented procedures and/or protocols to ensure compliance with REMS-defined requirements.

    b. The number and percentage of shipments that were shipped to non-enrolled healthcare facilities.

    c. The number and percentage of wholesalers/distributors identified in items 10(a-b) that successfully completed the required corrective and preventive action (CAPA) plan within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.

11. For the reporting period, the number of healthcare facility re-enrollments and the expected number of re-enrollments.

12. A summary of any approved or pending modifications to the REMS, since the last report, or if no such modifications, a statement of that fact.

13. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

The 6-month assessment will also include the following information:

a) The dates REMS materials became available to healthcare facilities 1) on the websites, and 2) via the call center.

b) The dates healthcare facility and wholesaler/distributor enrollment could successfully be completed 1) online, 2) by mail, and 3) by fax.

c) The dates the Adasuve REMS education program became available as 1) an in-service, and 2) online.

For the 12-month and all subsequent REMS assessments submitted annually thereafter, the following assessment will also be included:

1. Healthcare professional understanding of the serious bronchospasm risk and safe use conditions for Adasuve. If knowledge assessments indicate that awareness is inadequate, propose specific measures to increase awareness.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22549 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22549 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22549
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22549
REMS ASSESSMENT

PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

EXPIRY

A 24 month expiry date is granted based on the available stability data.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

SPECIAL REPORTING REQUIREMENTS FOR RESPIRATORY ADVERSE EVENTS

1. Continue to submit all initial and follow-up adverse drug experiences pertaining to respiratory events, including but not limited to the following: asthma, COPD, bronchospasm, wheezing, shortness of breath. Additionally, submit reports of respiratory events requiring intervention, such as treatment with a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (invasive and non-invasive), an emergency department visit/prolongation of an existing visit, or hospitalization/prolongation of an existing hospitalization as Postmarketing 15-day "Alert Reports" as defined under 21 CFR 314.80(c). We additionally remind you of your agreement, in your December 10, 2012 email, regarding obtaining follow-up information for case assessments of these findings as outlined in our letter dated December 6, 2012.

2. In the periodic reports submitted for the first quarterly reporting period and each subsequent reporting period, include the following:

   A summary and evaluation of all respiratory adverse events including but not limited to the following: preferred terms included in the Asthma/Bronchospasm SMQ, COPD, or Dyspnoea, as well as respiratory events requiring treatment with a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (invasive and non-

invasive), an emergency department visit/prolongation of an existing visit, or hospitalization/prolongation of an existing hospitalization.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

MITCHELL V Mathis
12/21/2012