DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022549/S-005

SUPPLEMENT APPROVAL

Alexza Pharmaceuticals, Inc.
Attention: Lily Gong
Director, Regulatory Affairs & Clinical Operations
2091 Stierlin Court
Mountain View, CA 94043

Dear Ms. Gong:

Please refer to your Supplemental New Drug Application (sNDA) dated December 22, 2015, received December 22, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adasuve (loxapine) inhalation powder, 10 mg.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated December 21, 2015.

This Prior Approval supplemental new drug application provides for proposed changes to the prescribing information and modifications to the approved risk evaluation mitigation strategy (REMS) for ADASUVE (loxapine). The currently approved prescribing information and Adasuve REMS requires certified healthcare settings (HCS) to have immediate access on-site to equipment and personnel trained to provide airway management, including intubation and mechanical ventilation. The proposed labeling changes, and corresponding REMS modifications, include removal of the requirement for on-site access to equipment necessary for advanced airway management. Instead, certified HCS must have immediate access on-site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. In addition, facilities must have a short-acting bronchodilator including a nebulizer and inhalation solution, for immediate treatment of bronchospasm.

The labeling changes consist of revisions to the Boxed Warning and Warning and Precautions sections of the Prescribing Information.

APPROVAL & LABELING

We have completed our review of this supplemental 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 note that your August 3, 2016, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for

assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Adasuve was originally approved on December 21, 2012, and the most recent modification was approved on December 9, 2013. 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 proposed modifications to the REMS consist of:

- Changes to the goal of the Adasuve REMS;
- Changes to the prescriber and healthcare setting attestations, and requirements for certified healthcare settings;

- Updates to the REMS materials to reflect the supplies and personnel that a certified healthcare setting must now have available to manage acute bronchospasm;
- Removal of the communication plan as an element of the REMS;
- Updates to reflect the change in ownership from Teva Pharmaceuticals to Alexza Pharmaceuticals, Inc.; and
- Updates to the implementation system to clarify your (Alexza Pharmaceuticals, Inc.) responsibilities.

Because the communication plan has been completed and the most recent assessment demonstrates that the REMS is fully implemented, we have determined that a communication plan is no longer necessary to include as an element of the approved REMS to ensure that the benefits of the drug outweigh the risks.

Your proposed modified REMS, submitted on December 22, 2015, amended on August 3, 2016, and appended to this letter, is approved.

The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on December 21, 2012.

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

For the current period and cumulatively:

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.

2. Educational program

    a. Number of educational materials distributed by field force and mail.

    b. Number of in-service educational programs offered and number of programs conducted

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

4. The number of patients who have received ADASUVE therapy

5. 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.

6. 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.

7. 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

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

9. 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).

10. 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.

11. The number and percentage of wholesalers/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.

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

13. 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.

14. 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 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 REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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.

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.

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

NDA 22549 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22549/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22549/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 22549/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22549/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 22549

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).
You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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, contact Danbi Lee, Regulatory Project Manager, at Danbi.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of 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
09/28/2016