NDA 022549/S-10

SUPPLEMENT APPROVAL

Alexza Pharmaceuticals, Inc.
Attention: Edwin Kamemoto, PhD
Regulatory Affairs
2091 Stierlin Court Mountain View, CA 94043

Dear Dr. Kamemoto:

Please refer to your supplemental new drug application (sNDA) dated January 13, 2021, received, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adasuve (loxapine) inhalation powder.

This Prior Approval supplemental new drug application proposes modifications to the approved Adasuve Risk Evaluation and Mitigation Strategy Requirements (REMS) as well as corresponding labeling revisions.

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for ADASUVE (loxapine) inhalation powder was approved on December 21, 2012 and the most recent REMS modification was approved on September 28, 2016. The REMS consists of 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 the following changes:

- adding that a short-acting bronchodilator (e.g., albuterol) by inhaler, with spacer, is an acceptable option to treat bronchospasm caused by Adasuve
- removal of the requirement to ensure all relevant staff are trained and replaced with a requirement that the healthcare setting have processes and procedures to ensure the safe use of Adasuve
- removal of the every 15 minute monitoring requirement
- removal of the need for post-dose chest auscultation
- conversion of the REMS Document to the new standardized format

In addition, the REMS goal was modified to reflect the above changes. The new goal is to mitigate the risk of negative outcomes (respiratory distress or respiratory arrest) associated with ADASUVE induced bronchospasm by:
Ensuring that ADASUVE is dispensed only in certified healthcare setting that have:

a) Immediate access on site to supplies and healthcare professionals competent in the management of acute bronchospasm and access to emergency assistance for symptoms that require immediate medical attention. Healthcare settings must have a short-acting bronchodilator (e.g., albuterol), for the immediate treatment of bronchospasm; this short-acting bronchodilator can be delivered by inhaler (with spacer) or nebulizer.

b) Processes and procedures to ensure that patients are screened for conditions for which Adasuve is contraindicated and monitored for signs of bronchospasms.

Your proposed modified REMS, submitted on January 13, 2021, amended on September 15, 2021 and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to annually from the date of approval of the REMS modification (01/27/2022).

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

Program Implementation and Operations

1. REMS Certification Statistics (per reporting period and cumulatively)
    a. Healthcare Settings
        i. Number of newly certified, (first certified during the reporting period), total certified (in a certified status at any time during the reporting period), and active (i.e., have received Adasuve) healthcare settings stratified by healthcare setting type and geographic US Census region
2. Adasuve Utilization Data (per reporting period and cumulatively)
    a. Describe the method used to estimate Adasuve utilization.
    b. Number of doses distributed to certified healthcare settings
    c. Number of estimated unique patients receiving Adasuve, stratified by healthcare setting type.
    d. Number of active and certified healthcare settings that ordered and received shipments of Adasuve during the reporting period and cumulatively
3. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)
    a. REMS Call Center
        i. The number of calls received by the REMS Call Center, stratified by stakeholder type (patient, healthcare provider, healthcare setting, other), accompanied by description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls)
        ii. The number of REMS Program issues/complaints reported to the REMS Call Center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls) and the resolution (if applicable)
        iii. A summary and analysis of calls that may indicate an issue with patient access, or burden on the healthcare delivery system
        iv. A summary of corrective actions resulting from issues identified through the REMS Call Center
4. REMS Compliance (per reporting period and cumulatively)

Provide a summary of non-compliance identified, including but not limited to:

a. Provide a copy of the non-compliance plan, including the criteria for noncompliance for each stakeholder, actions taken to address non-compliance for each case, and which event led to decertification from the REMS.

b. Provide a copy of the audit plan for each stakeholder (healthcare settings and wholesalers/distributors) (for cause audits, as needed)

c. Report of audit findings for each stakeholder

i. The number of audits expected, and the number of audits performed

ii. The number and types of deficiencies (i.e., minor, moderate, serious) noted for each group of audited stakeholders

iii. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within 30 calendar days of the audit.

iv. For any that did not complete the CAPA within 30 calendar days of the audit, describe actions taken.

v. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.

vi. Key Performance Indicator: A total of 99% of healthcare settings have documented procedures and protocols to ensure compliance with the REMS safe use conditions out of the total number of audited healthcare settings.

vii. Number and percentage that lacked documented procedures and protocols to ensure compliance with the following REMS safe use conditions out of the total number of audited stakeholders.

1) The healthcare setting is equipped with the necessary supplies and personnel to manage acute bronchospasm and ready access to emergency response services. Healthcare settings must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.

2) Screen patients prior to treatment with Adasuve, for a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other lung disease associated with bronchospasm, acute respiratory signs/symptoms (e.g., wheezing), and current use of medications to treat airways disease such as asthma or COPD.

3) Examine patients (including chest auscultation) for respiratory abnormalities.

4) Monitor patients for a minimum of one hour following treatment with Adasuve for symptoms and signs of bronchospasm

5) Limit administration of Adasuve to a single dose per patient within a 24-hour period.

6) Adasuve is not dispensed for use outside of the authorized representative's certified healthcare setting.

7) Do not sell, loan, or transfer any Adasuve inventory to any other pharmacy, institution, distributor, or prescriber.

viii. Provide number of designated authorized representatives who have changed since enrollment.

d. Healthcare settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)

i. The number and type of healthcare settings for which non-compliance with the REMS is detected

ii. Number and type of non-certified healthcare settings that administered ADASUVE and the number of incidents for each setting

iii. Number of times where healthcare settings dispensed ADASUVE to outpatients out of the total number of dispenses

iv. Number of times Adasuve was distributed, transferred, or loaned from one healthcare setting to another

v. Number and percentage of healthcare settings that lacked immediate-access on site to supplies (bronchodilator) to ensure compliance with the REMS safe use conditions out of the total number of healthcare settings

vi. Number of healthcare settings deactivated for non-compliance and reasons for deactivation out of the total number of healthcare settings

e. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)

i. Number of authorized wholesalers/distributors for which non-compliance with the REMS is detected out of the total number of wholesalers/distributors

ii. Number of instances where ADASUVE was shipped to non-certified entities out of the total number of shipments

iii. Number and percentage of shipments that were shipped to a non-certified healthcare setting or directly to patients. out of the total number of shipments

Health Outcomes and/or Surrogates of Health Outcomes

5. Safety Surveillance (per reporting period and cumulatively)
    a. Known, or suspected adverse events related to bronchospasm and other respiratory adverse events
        i. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
        ii. Include a line listing of all cases that includes manufacturer control number, narrative, assessment of causality, and source of the report
        iii. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication
6. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect of 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 one 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 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 that 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 rational 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 a REMS modification*, 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 022549 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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 022549 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022549/S-
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022549/S-

PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022549/S-
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022549/S-
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 REVISION FOR NDA 022549

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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 Ermias Zerislassie, Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - o Prescribing Information
  - o Medication Guide
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC B STONE
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