Risk Evaluation and Mitigation Strategy (REMS) Document
Adasuve (loxapine) REMS Program

I. Administrative Information

Application Number: NDA 022549
Application Holder: Alexza Pharmaceuticals, Inc.
Initial REMS Approval: 12/2012
Most Recent REMS Update: 01/2022

II. REMS Goal

The goal of the ADASUVE REMS is to mitigate the risk of negative outcomes (respiratory distress or respiratory arrest) associated with ADASUVE induced bronchospasm by:

1) 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.

III. REMS Requirements

Alexza Pharmaceuticals, Inc. must ensure that healthcare settings, patients, and wholesalers-distributors comply with the following requirements
**1. Healthcare settings that dispense ADASUVE must:**

<table>
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<tr>
<th>To become certified to dispense</th>
<th>1. Have immediate access to supplies and personnel onsite competent in the management of acute bronchospasm including: a short-acting bronchodilator (e.g., albuterol), delivered by inhaler (with spacer) or nebulizer, and access to emergency assistance for symptoms that require immediate medical attention.</th>
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<td>2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.</td>
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<td>3. Have the authorized representative review the Education Program for Healthcare Settings.</td>
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<td>4. Have the authorized representative enroll in the REMS Program by completing the Healthcare Settings Enrollment Form and submitting it to the REMS Program.</td>
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<td>5. Establish processes and procedures to verify (1) the patient is assessed for respiratory abnormalities before administration (by medical history, medication history, and chest auscultation), (2) the patient is assessed for a minimum of 1 hour after administration for bronchospasm, (3) no more than a single dose of ADASUVE is administered within a 24-hour period, (4) ADASUVE is not dispensed outside of the certified healthcare setting.</td>
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<th>Before administering</th>
<th>6. Assess the patient’s health status 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 airway disease such as asthma or COPD.</th>
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<td>7. Assess the patient’s health status for respiratory abnormalities by chest auscultation.</td>
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| After administering, for a minimum of 1 hour | 8. Assess the patient’s health status for signs and symptoms of bronchospasm. |

| During treatment, within a 24-hour period | 9. Dispense no more than a single dose per patient. |

| To maintain certification to dispense | 10. Have any new Authorized Representative enroll in the REMS Program by completing the Healthcare Setting Enrollment Form and submitting to the REMS Program. |

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<th>At all times</th>
<th>11. Not dispense ADASUVE for use outside of the certified healthcare setting.</th>
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<td>12. Report any adverse events of bronchospasm that occur following ADASUVE treatment to the REMS Program.</td>
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<td>13. Not distribute, transfer, loan or sell ADASUVE.</td>
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<td>14. Maintain appropriate documentation that all processes and procedures are being followed for the Adasuve REMS Program.</td>
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<td>15. Comply with audits by Alexza Pharmaceuticals, Inc., or a third party acting on behalf of Alexza Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.</td>
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2. Patients who are prescribed ADASUVE:

Before treatment initiation
1. Be monitored for signs and symptoms of breathing problems.
2. Complete a medical history and medication history with the prescriber.

During treatment; for at least 1 hour
3. Be monitored for signs and symptoms of bronchospasm.

3. Wholesalers-distributors that distribute ADASUVE must:

To be able to distribute
1. Establish processes and procedures to ensure that the drug is distributed only to certified healthcare settings.
2. Train all relevant staff involved in distributing ADASUVE.

At all times
3. Distribute only to certified healthcare settings.
4. Maintain records of distribution including all shipments of ADASUVE.
5. Comply with audits by Alexza Pharmaceuticals, Inc., or a third party acting on behalf of Alexza Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and being followed.

Alexza Pharmaceuticals, Inc. must provide training to healthcare settings that dispense ADASUVE

The training includes the following educational materials: Education Program for Healthcare Settings. The training must be available online and in print format.

To support REMS Program operations, Alexza Pharmaceuticals, Inc. must:

1. Establish and maintain a REMS Program website, www.adasuverems.com. The REMS Program website must include the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).

2. Make the REMS Program website fully operational and all REMS materials available through the website or ADASUVE REMS Program Call Center within 60 calendar days of REMS modification (01/27/2022).

3. Establish and maintain a REMS Program call center for REMS participants at 855-755-0492.

4. Establish and maintain a validated and secure database of all REMS participants who are enrolled and/or certified in the ADASUVE REMS Program.

5. Ensure healthcare settings are able to enroll online, by email and fax.

6. Provide authorized wholesalers-distributors access to the database of certified healthcare settings.

7. Provide Education Program for Healthcare Settings, Healthcare Setting Enrollment Form, and the Prescribing Information to healthcare settings who (1) attempt to order ADASUVE and are not yet certified or (2) inquire about how to become certified.

8. Notify healthcare settings within 2 business days after they become certified in the REMS Program.
To ensure REMS participants’ compliance with the REMS Program, Alexza Pharmaceuticals, Inc. must:

9. Verify annually that the authorized representative’s name and contact information correspond to those of the current designated authorized representative for the healthcare setting. If different, the healthcare setting must be required to re-certify with a new authorized representative.

10. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of ADASUVE distribution; certification of healthcare settings; and audits of REMS participants. These records must be readily available for FDA inspections.

11. Establish a plan for addressing noncompliance with REMS Program requirements.

12. Monitor healthcare settings and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

13. Audit all healthcare settings within 180 calendar days after they become certified and have received at least one shipment, and every 3 years thereafter, to ensure that all REMS processes and procedures are in place, functioning and support the REMS Program requirements. To be audited, a healthcare setting must have received at least one shipment of ADASUVE in the past 12 months.

14. Audit wholesalers-distributors no later than one year after the wholesaler-distributor is authorized and at least one every calendar year to ensure that all REMS processes and procedures are in place, functioning and support the REMS Program requirements.

15. Take reasonable steps to improve operations of and compliance with the requirements in the ADASUVE REMS Program based on monitoring and evaluation of the ADASUVE REMS Program.

IV. REMS Assessment Timetable

Alexza Pharmaceuticals, Inc. must submit REMS assessments annually from the date of approval of the REMS modification (01/27/2022). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Alexza Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the ADASUVE REMS:

**Enrollment Forms**
Healthcare Setting:

1. Healthcare Setting Enrollment Form

**Training and Educational Materials**
Healthcare Setting:

2. Education Program for Healthcare Setting

**Other Materials**

3. REMS website (www.adasuverems.com)