

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022549Orig1s000

RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Psychiatry Products**

NDA/BLA #s: 022549
Products: ADASUVE (loxapine) inhalation powder
APPLICANT: Alexza Pharmaceuticals
FROM: Mitchell V. Mathis, M.D., Director (acting), Division of Psychiatry Products
DATE: December 4, 2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes a communication plan and elements to assure safe use is necessary for Adasuve (loxapine) inhalation powder to ensure that the benefits of the drug outweigh the risks of the negative outcomes associated with Adasuve-induced bronchospasm. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States with agitation associated with schizophrenia or bipolar I disorder:

Approximately 4 million patients per year in the U.S. experience an episode of acute agitation associated with schizophrenia or bipolar I disorder. Agitation is a serious medical problem that can present in a number of psychiatric disorders, including schizophrenia and bipolar disorder. Schizophrenia affects approximately 2.4 million adults in the United States, and bipolar disorder affects approximately 5.7 million adults in the United States, according to National Institutes of Mental Health (NIMH) prevalence rates. According to the World Health Organization (2003), schizophrenia affects approximately 1% of the population worldwide, and bipolar disorder affects 1-2% of the population worldwide. All patients with schizophrenia or bipolar disorder are at risk for acute agitation. (b) (4)

However, it is not possible to precisely estimate the population likely to use Adasuve (loxapine).

B. The seriousness of the disease or condition that is to be treated with the drug:

Agitation is a severe, disruptive, and morbid complication of schizophrenia (Osser and Sigadel, 2001) and mania (Alderfer and Allen, 2003). Agitation can be defined as a state of motor restlessness accompanied by mental tension. Symptoms of agitation can include excitement, physical and verbal hyperactivity, hostility, and aggression. Symptoms can escalate quickly and unpredictably resulting in violent behavior and pose a considerable risk to both patients and those around them. Signs of mounting tension can include pacing, hand wringing, intense staring, clenching fists, pressured speech, mutism, yelling, banging objects, or threatening others (Battaglia, 2005). Acute agitation associated with psychiatric diseases is one of the most important contributors to the continued stigmatization of mental illness (Buckley, 1999). It results in severe distress in patients themselves, and in disruption of the lives of those who care for or live with them.

C. The expected benefit of the drug with respect to such disease or condition:

Adasuve (loxapine) is an important new therapeutic option for the management of acute agitation. It can provide: 1) a rapid onset of action (within approximately 10 minutes after dosing). Adasuve (loxapine) is delivered by oral inhalation immediately to the deep lung and absorbed rapidly; the rate of drug delivery is similar to that with an intravenous injection, 2) an easily administered dosage form; 3) a non-invasive treatment option. Adasuve (loxapine) would be an alternative to intramuscular formulations of antipsychotics, which can be associated with physical injury (to the patient and healthcare professionals) during restraint, as well as needle stick injury. Because they often require physical restraint, intramuscular injections are often viewed by patients and healthcare professionals as being coercive. Adasuve (loxapine) would be an alternative treatment that could assist patients and healthcare providers maintain a therapeutic alliance and involve the patient in decision making about treatment.

Currently, three atypical antipsychotics (aripiprazole, ziprasidone, and olanzapine) have been approved for intramuscular treatment of agitation associated with schizophrenia or bipolar disorder. Benzodiazepines and first generation antipsychotics are also used (orally or parenterally) off-label. While the efficacy of these medications has been demonstrated, the onset of clinically meaningful anti-agitation effects typically occurs 30 to 60 minutes after oral administration and up to 30 minutes after intramuscular administration (Breier et al, 2001; Kinon et al, 2004; Tran-Johnson et al, 2007). This leaves a significant period during which patients, staff, and property remain vulnerable to the deleterious behaviors associated with agitation. In addition, patients may resist intramuscular treatment, which can present risks to caregivers, such as needle-stick injuries.

The rapid onset and proven efficacy of Adasuve (loxapine) will quickly prevent escalation of agitation symptoms, decreasing the likelihood of injuries to the patient or medical personnel associated with having to physically restrain the patient. Since Adasuve (loxapine) is a

noninvasive treatment, its use could avoid injuries associated with needle sticks, especially in an acutely agitated patient.

The therapeutic alliance between an agitated patient and the treatment team can be strengthened by allowing the patient to be more involved in treatment decisions. By presenting the options of the inhalable product, injections, or orals, the patient can have some choice, and the healthcare provider can avoid coercion and the danger of wrestling with patients and forcibly injecting them. In fact, establishing a better relationship with the patient can, in itself, help de-escalate agitation and violent behavior.

D. The expected or actual duration of treatment with the drug:

Adasuve (loxapine) is expected to be used in hospital and emergency room settings for the treatment of acutely agitated patients with schizophrenia or bipolar I disorder. Because agitation associated with schizophrenia and bipolar disorder is an acute and intermittent condition, it is anticipated that patients will be treated with Adasuve (loxapine) on an infrequent basis.

E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug:

The primary safety concern associated with Adasuve (loxapine) is pulmonary toxicity, primarily bronchospasm. The risk is increased in patients with asthma or chronic obstructive pulmonary disease (COPD). The sponsor has conducted pulmonary safety studies in subjects with asthma and COPD. In the asthma study, 69% of loxapine-treated subjects compared to 12% of placebo-treated subjects had notable respiratory signs or symptoms, defined as FEV1 decrease from baseline of $\geq 20\%$, an airway adverse event (AE), or use of rescue medication. The most common airway AEs in loxapine-treated subjects in the asthma study were bronchospasm (~27%), chest discomfort (~23%), wheezing (~15%), and dyspnea (11.5%). In the COPD study, approximately 58% of loxapine-treated subjects had notable respiratory signs or symptoms compared to approximately 22% of placebo-treated patients. The most common airway AEs in loxapine-treated subjects in the COPD study were dyspnea (11.5%), cough (11.5%), and wheezing (~8%).

Adasuve (loxapine) is contraindicated in patients with a history of asthma, COPD, or other lung diseases associated with bronchospasm, because they are at increased risk of bronchospasm. Adasuve (loxapine) is contraindicated in patients with acute respiratory signs or symptoms (e.g., wheezing) and in patients who are using medications to treat airways disease, such as asthma or COPD. In the short-term, placebo-controlled, pivotal efficacy trials of acutely agitated patients with schizophrenia and bipolar disorder, patients with clinically significant acute or chronic pulmonary disease were excluded. However, two subjects (0.8%) who received loxapine developed wheezing which did not require treatment, and one patient (0.4%) developed bronchospasm which resulted in early discontinuation and required bronchodilator treatment. It is not possible to precisely estimate the incidence of bronchospasm in the population likely to use Adasuve (loxapine).

F. Adasuve (loxapine) is not a new molecular entity.

The elements of the REMS will be a communication plan, elements to assure safe use (ETASU), including that healthcare settings that dispense Adasuve be specially certified, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS is intended to mitigate the negative outcomes associated with Adasuve-induced bronchospasm by ensuring that Adasuve is dispensed only in certified healthcare settings that have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation; informing healthcare professionals in these settings that Adasuve can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest; and informing healthcare professionals in these settings about the safe use of Adasuve, including appropriate patient selection, monitoring, and management..

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/s/

KIMBERLY S UPDEGRAFF
12/20/2012

MITCHELL V Mathis
12/21/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Addendum to Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: December 19, 2012

Reviewer(s): Kimberly Lehrfeld, Pharm.D., Risk Management Analyst
Division of Risk Management

Team Leader: Reema Mehta, Pharm.D., M.P.H.
Division of Risk Management

Division Director: Claudia Manzo, Pharm.D.
Division of Risk Management

Drug Name(s): Adasuve[®] (loxapine *Staccato* inhalation powder)

Therapeutic Class: Antipsychotic

Dosage and Route: 10mg single dose inhaler

Application Type/Number: NDA 22549

Applicant/Sponsor: Alexza Pharmaceuticals, Inc.

OSE RCM #: 2011-2957

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

This is an addendum to the Division of Risk Management (DRISK) Final Risk Evaluation and Mitigation Strategy (REMS) review, dated April 2, 2012, for Adasuve® (loxapine *Staccato* inhalation powder). This review provides the revision history of the Adasuve REMS materials since April 12, 2012 and includes the final, agreed upon Adasuve REMS document and Adasuve REMS materials.

1.1 REGULATORY HISTORY

On April 12, 2012, the Agency provided the Sponsor with edits to the Adasuve REMS and associated REMS documents (submitted 27 March 2012, Seq. No. 0039) via email. A summary of the revisions provided to the Sponsor is as follows:

REMS Document:

- Include an additional attestation statement that certified healthcare facilities (HCFs) will not sell, loan or transfer any Adasuve inventory to any other pharmacy, institution, distributor, or prescriber. In addition, as recommended by the Office of Compliance (OC), two certified HCF attestations were clarified by adding that “Prior to ordering Adasuve” the HCF must have policies and procedures in place to meet the requirements of the REMS and must have trained all relevant staff as required by the REMS because no timeframe was proposed for meeting these requirements.
- Remove (b) (4) and replace with an attestation they “will ensure that there are policies and procedures in place to ensure Adasuve is only distributed to health care facilities in which enrollment in the Adasuve REMS program has been validated.”
- FDA requested Alexza respond by April 13, 2012 by submitting the revised REMS via email if they were in agreement with the proposed changes in the attestations.

Dear Healthcare Professional (DHCP) Letter

- Revised the letter to focus the safety messages to the following:
 - Risk of Bronchospasm with ADASUVE
 - To Administer ADASUVE, Healthcare Facilities Must Enroll in the ADASUVE REMS Program

HCF Enrollment Information and Enrollment Form

- Add a field to record facility DEA or NPI number
- Increase the font size of the attestation statements
- Align attestation statements with changes in the REMS document (see above: REMS document, bullet 1)

Wholesaler/Distributor Enrollment Form

- Changed attestation statements to reflect new attestations in the REMS document (see above: REMS document, bullet 2)

Steps for Safe Use of Adasuve

- Added a statement reminding HCPs that, in addition to asking patients about a medical history of pulmonary disease and current medications to treat pulmonary disease, they should also check medical records if available.

Order Set/Protocol Template

- Added check boxes for signs and symptoms of pulmonary abnormalities during screening before Adasuve administration and during monitoring after Adasuve has been administered.
- Included specifying chest auscultation monitoring every 15 minutes after Adasuve administration.

Healthcare Provider Brochure

- Aligned language in document with the current prescribing information (PI) language. This included updating the Indications, Contraindications, Boxed Warning, Dosing and Administration and Instructions for Use (IFU) sections.
- Updated Steps for Safe Use in this document to align with recommendations above (see above: Steps for Safe Use)
- Edited the text of “Prescribing and Administering Adasuve at Your Healthcare Facility” to be clearer about HCF requirements in order to become enrolled in the Adasuve REMS program.

Adasuve Education Program

- Updated text to align with PI for Adasuve including current IFU text and diagrams.
- Advised sponsor to include information about albuterol use and bronchospasm occurrence after both doses of Adasuve. This data can be presented in table or bulleted form.
- Advised sponsor to provide a graph figure describing the “Change from Baseline in FEV1 in Subjects with Asthma” on Slide 13 that is the same graph figure included in the PI.
- Updated Steps for Safe Use in this document to align with recommendations above (see above: Steps for Safe Use)

REMS Supporting Document:

- Updated Adasuve REMS Supporting Document to reflect the current REMS document and labeling.
- Advised the sponsor to expand the REMS Supporting Document to include explanations of the following REMS assessment and audit information:

- The methods used to ensure that the person enrolling the healthcare facility is, in fact, authorized to do so.
- The audit plans for healthcare facilities and for wholesalers/distributors, including strategy for identifying facilities and wholesalers to be audited.
- The plans for ensuring all forms are complete prior to enrolling a healthcare facility or distributor.
- Plans for providing in-service education
- Methods for ensuring that HCFs do not transfer Adasuve.

On April 13, 2012, Alexza emailed the Adasuve REMS document to FDA, which acknowledge acceptance of the changes to the attestation statements proposed in the email dated April 12, 2012. (see above:REMS document, bullet 1)

On April 18, 2012, the Agency communicated additional revisions to the Instructions for Use sections of the Adasuve REMS Education Program and the Provider Brochure (submitted March 27, 2012, Seq. No. 0039) via email. Furthermore the Agency provided a document with the proposed REMS Assessment Plan. The Agency advised the Sponsor to incorporate the Assessment Plan into the REMS Supporting document.

On April 19, 2012, after internal discussion between Division of Psychiatry Products (DPP), DRISK, and Division of Pharmacovigilance (DPV), it was agreed that in order to promote adverse event (AE) reporting at certified HCFs, additional language should be added to the REMS and REMS materials about the importance of AE reporting. Therefore, the Agency provided the Sponsor with revisions to the REMS document and HCF Enrollment Form, which included the addition of an attestation statement that certified HCFs understand the importance of reporting serious adverse events associated with Adasuve. In addition, additional language regarding adverse event reporting was added to the Healthcare Provider brochure and the Adasuve Education Program.

On April 21, 2012, Alexza emailed the revised Adasuve REMS document and all other REMS materials to FDA in response to comments emailed on April 12, 2012, April 18, 2012, and April 19, 2012.

Below is a summary of Alexza's concurrence and additional proposed revisions to all REMS documents:

- All FDA edits and changes were accepted by Alexza with only minor changes in the following documents: REMS document, HCP Brochure, HCF enrollment form, Order Set/Protocol Template, DHCP letter, Steps for Safe Use, and REMS Supporting Document
- All FDA proposed changes to the Education Program were accepted. Alexza proposed the following additional changes.

-  (b) (4)

On September 28, 2012 (Seq. No. 0048), Alexza resubmitted all REMS documents which reflected labeling as of September 21, 2012.

The Sponsor made the following major edits to the documents:

Adasuve Education Program:

REMS Supporting Document:

- The Sponsor updated the “Audit Plan and Strategy for Facilities and Wholesalers” and “Periodic Audits of the Distribution Database” on pages 35-36 of the Supporting document. OC was consulted on the Sponsors edits and made recommendations on October 25, 2012, in an addendum to their original REMS Memorandum, dated March 30, 2012. Their recommendations were incorporated in the edited REMS Supporting document, communicated to the Sponsor on November 14, 2012 via email.

Furthermore, the Sponsor made the following minor edits to the documents

- Throughout all documents, the Sponsor added the appropriate trademarks.
- Other minor editorial changes that did not impact the risk message or the REMS.

On November 14, 2012, FDA emailed all proposed REMS documents to Alexza with recommendations noted above.

On November 21, 2012 (Seq. No.0051), Alexza resubmitted the REMS documents.

On December 4, 2012, FDA emailed the following comments to the Sponsor:



- Edits to the Assessment Plan.



On December 7, 2012 (Seq. No. 0052), Alexza accepted the recommendations of FDA emailed on December 4, 2012 and submitted all REMS documents, except for the REMS supporting document, in one PDF file.

On December 14, 2012, The Office of Regulatory Policy (ORP) and The Office of Chief Counsel (OCC) provided comments on the REMS document.



On December 17, 2012, after consultation with DPP, ORP and OCC, a communication plan (CP) was added to the REMS to include the DHCP letter. FDA and Alexza met via teleconference to discuss the addition of the CP as well as the following changes to the REMS document and REMS materials, which were recommended by ORP and OCC during the clearance process:

- Addition of Section II.A. Communication Plan to the Adasuve REMS document. The Communication Plan includes a DHCP letter which will be distributed once, at least 2 weeks prior to launch of Adasuve.

As a result, the REMS Supporting Document was revised to reflect this change.

- ORP recommended the addition of the clarifier “per patient” be added to the following attestation. Without the clarifier it limits the HCF to dispensing only one Adasuve at the healthcare facility within a 24-hour period.

II.B.1.e.

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

As a result, the following REMS materials were revised:

- Healthcare Facility Enrollment Information and Form
- Adasuve Education Program
- Healthcare Provider Brochure

- OCC recommended the following statement be removed from the REMS document.



As a result, the following REMS materials were revised:

- Wholesaler/Distributor Enrollment Form
- Adasuve REMS Website

- REMS Supporting Document

The following edits were made to the REMS Assessment Plan (5.b.)

- Item 9 contained 2 separate items. These must be separated into Item 9 and Item 10.
- Item number 9 text refers to item 9 (a-c) instead of item 8 (a-c).

During the teleconference, Alexza verbally concurred with the proposed changes and agreed to resubmit the REMS document and all REMS materials in both word and PDF format by December 19, 2012.

On December 19, 2012 (Seq. No. 0054), Alexza submitted the final version of the REMS document, REMS Supporting Document and all REMS materials as individual word documents and PDF documents.

2 MATERIALS REVIEWED

2.1 MATERIALS REVIEWED

The following materials, received December 19, 2012 (Seq. No.0054) were reviewed:

- ADASUVE REMS document
- Healthcare Facility Enrollment Information and Form
- Dear Healthcare Professional Letter
- Healthcare Provider Brochure
- Steps for Safe Use of ADASUVE
- Order Set/Protocol Template
- ADASUVE Education Program
- ADASUVE REMS website (www.adasuverems.com)
- Wholesaler/Distributor Enrollment Form
- ADASUVE REMS Supporting Document

2.2 ANALYSIS TECHNIQUES

The REMS proposal was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and responsiveness to Agency comments.

3 RESULTS OF REVIEW OF PROPOSED ADASUVE RISK EVALUATION AND MITIGATION STRATEGY

3.1 ADASUVE REMS ASSESSMENT PLAN

For the current period and cumulatively, the intent is to include the following in the REMS assessment:

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.

In addition, the 6-month assessment will include the following information:

1. The dates REMS materials became available to healthcare facilities 1) on the websites, and 2) via the call center.
2. The dates healthcare facility and wholesaler/distributor enrollment could successfully be completed 1) online, 2) by mail, and 3) by fax.
3. 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, the following assessment will 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.

4 DISCUSSION AND CONCLUSION

During this review period, only changes to refine the risk messages and content of the Adasuve REMS were included. The focus of the second cycle Adasuve REMS review was to finalize the REMS Assessment and Audit Plan, (b) (4) (b) (4) revise the attestations statements to align with the requirements of the program, move the DHCP letter under a communication plan, and update all REMS materials to reflect final Adasuve Prescribing Information.

In conclusion, the amended REMS for Adasuve (loxapine Staccato inhalation powder), December 19, 2012 contains the appropriate and agreed upon revisions as stipulated by the Agency on December 19, 2012. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Adasuve REMS in achieving the goals.

Therefore, the Adasuve REMS is compliant under FDAAA and acceptable to the Office of Medication Error Prevention and Risk Management, the Division of Risk Management.

5 RECOMMENDATIONS

The Office of Medication Error Prevention and Risk Management, DRISK recommends approval of the Adasuve REMS December 19, 2012.

In addition, we recommend the ADASUVE REMS Assessment Plan (Section 3.1) be included in the REMS Section of the Approval Letter.

ATTACHMENTS

1. ADASUVE REMS document
2. Healthcare Facility Enrollment Information and Form
3. Dear Healthcare Professional Letter
4. Healthcare Provider Brochure
5. Steps for Safe Use of ADASUVE
6. Order Set/Protocol Template
7. ADASUVE Education Program
8. ADASUVE REMS website (www.adasuverems.com)
9. Wholesaler/Distributor Enrollment Form
10. ADASUVE REMS Supporting Document

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/s/

KIMBERLY LEHRFELD
12/19/2012

CLAUDIA B MANZO
12/19/2012
concur



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance

REMS Memorandum

TO: Thomas P. Laughren, MD., Director
Division of Psychiatry Products

THROUGH: Tamika White, Acting Branch Chief
Post Marketing Safety Brach
Division of Safety Compliance
Office of Compliance (OC)

FROM: Kendra Biddick, Consumer Safety Officer
Post Marketing Safety Brach, REMS Compliance Team
Division of Safety Compliance
Office of Compliance (OC)

SUBJECT: Risk Evaluation and Mitigation Strategy (REMS) Review

NDA 022549

This memorandum is the OC review of the Adasuve (loxapine) inhalation powder, NDA 022549, REMS submitted by Alexza Pharmaceuticals, Inc. to the Food and Drug Administration (FDA) on January 10, 2012, and revised by the Office of Surveillance and Epidemiology on February 16, 2012.

BACKGROUND

Loxapine is a first generation, typical antipsychotic. Loxapine inhalation powder is formulated as a single-dose, inhaled powder which is vaporized and delivered via the Staccato device. Alexza Pharmaceuticals is seeking approval of loxapine inhalation powder for the acute treatment of agitation associated with schizophrenia and bipolar disorder.

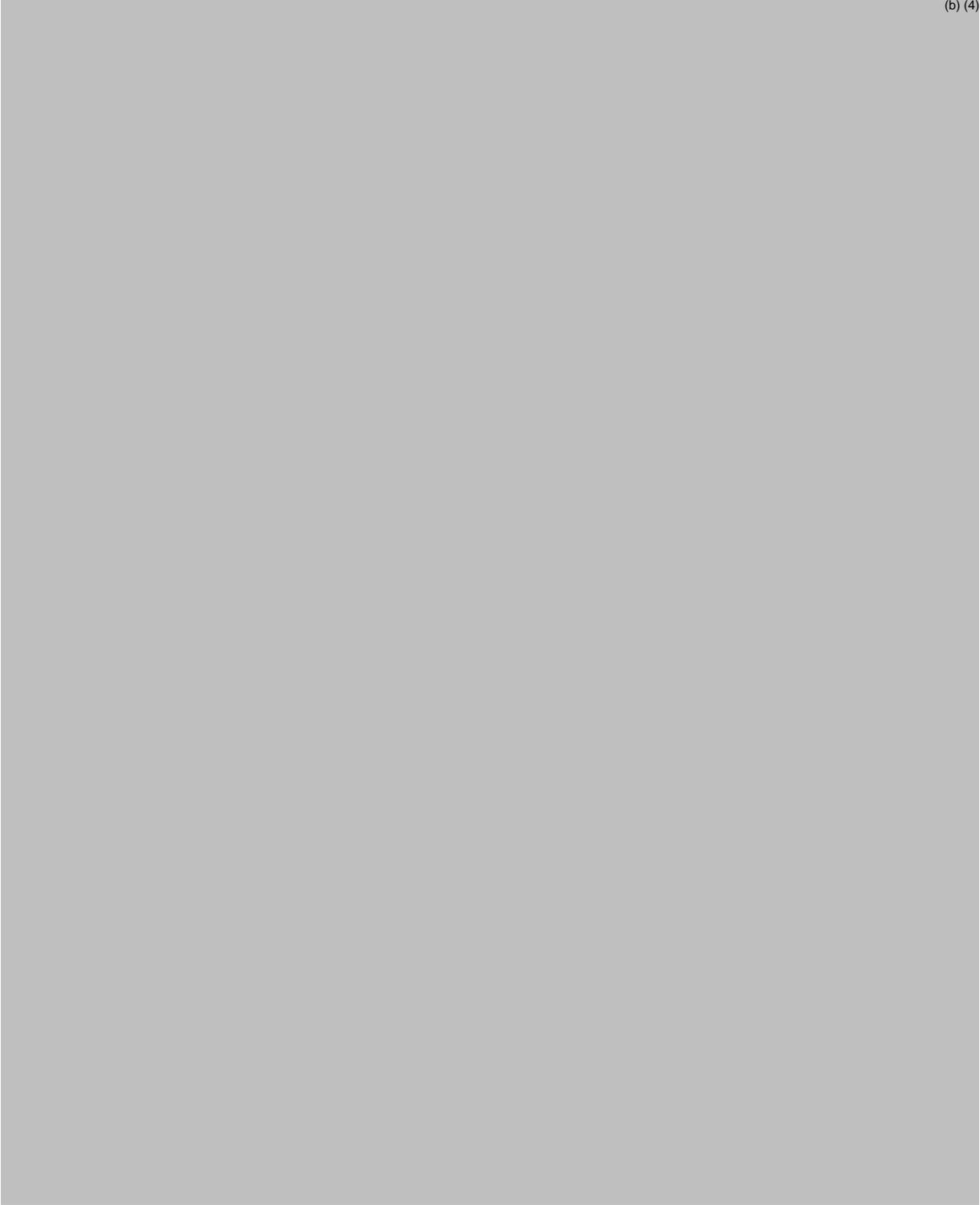
Loxapine inhalation powder via the Staccato device provides a non-invasive method of treatment for agitation, but is associated with a serious pulmonary adverse event. The primary safety issue is the risk of acute bronchospasm. This risk is increased in patients with underlying airway hyper responsiveness, including asthma and chronic obstructive pulmonary disease (COPD).

In meetings between the Division of Psychiatry Products (DPP), the Office of Surveillance and Epidemiology, and OC, DPP has been very clear that in order to prevent deaths, healthcare facilities must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

Review date: November 1, 2012

On February 16, 2012, FDA sent an email to Alexza Pharmaceuticals which included a REMS document that DRISK had drafted. This review provides comments to the February 16, 2012 REMS, to improve the enforceability of the REMS for Adasuve.

OC OBSERVATIONS (bold italics added to highlight points of interest)



(b) (4)



OC RECOMMENDATIONS

Recommendations to Alexza via the Office of Surveillance and Epidemiology and the Division of Psychiatry Products should include the following:



ADDENDUM: OCTOBER 25, 2012

All Office of Compliance concerns have been adequately addressed. Compliance and OSE agreed on the following REMS assessment and audit plans.

a) REMS Assessments

For the current period and cumulatively, the intent is to include the following in the REMS assessment:

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:
 - was not enrolled
 - was dis-enrolled due to non-compliance with the REMS.
 - 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 9 (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. 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.
10. For the reporting period, the number of healthcare facility re-enrollments and the expected number of re-enrollments.
 11. 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.
 12. 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.

In addition, the 6-month assessment will include the following information:

1. The dates REMS materials became available to healthcare facilities 1) on the websites, and 2) via the call center.
2. The dates healthcare facility and wholesaler/distributor enrollment could successfully be completed 1) online, 2) by mail, and 3) by fax.
3. 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, the following assessment will be included:

Healthcare provider 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.

If it is determined that corrective action is required, the following potential options to address deficiencies include:

- Resend REMS materials
- Offer to provide retraining on REMS Program and ADASUVE Education Program
- Assess adequacy of training materials and modify as needed

b) Audit Plan and Strategy for Facilities and Wholesalers

Alexza will perform routine audits of healthcare facilities and wholesale/distributors that are administering or dispensing ADASUVE utilizing established auditing methods. An audit protocol, including a matrix for site selection, sample size selection and audit frequency, auditor training plan, and an audit data collection form will be developed.

The rationale for healthcare facility selection at each audit interval will be based upon sampling sites that are distributed geographically, that have varying volumes of ADASUVE use (i.e., high, medium, low), and that cover the spectrum of different types of facilities that will be administering ADASUVE (i.e. emergency room, psychiatric emergency room and psychiatric in-patient unit). Each year the selection will consist of 10% of all participating healthcare facilities.

For wholesaler/distributor selection, all three (100%) wholesalers/distributors will be audited in year one. Thereafter, at least one wholesaler will be audited every calendar year. Audits will be conducted through onsite visits, responses to surveys and/or from other data feeds to assess healthcare facility and wholesale/distributor compliance with the ADASUVE REMS requirements. The data sources for these audits may include, but may not be limited to, the following:

- Facility's Qualification Documentation
- Policy and Procedure Review
- Training Verification (e.g. signature logs with associated curriculum)
- Facility Systems for product inventory (e.g. pharmacy database)
- Records documenting corrective actions that have been taken
- Wholesaler shipment records

Audit findings and corrective actions will be included as part of scheduled REMS assessment reports. All audited facilities that had critical or serious observations will be re-audited within one year, to ensure that corrective and preventative action plans were completed.

d) Periodic Audits of the Distribution Database

Audits will be completed to ensure that Wholesaler/Distributors are only distributing ADASUVE to enrolled healthcare facilities.

- Periodic audits of enrolled healthcare facility policies, procedures and order sets, and training records

Ten percent of all enrolled healthcare facilities will be audited annually. Audits will include, at a minimum, documentation that certified healthcare facilities have:

- Trained healthcare facility staff on the safe use of ADASUVE, as described in the ADASUVE REMS Education Program and maintained training records
- Established policies, procedures, and order sets to help ensure compliance with the safe use conditions required in the ADASUVE REMS.

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/s/

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11/05/2012

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11/09/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 02, 2012

Reviewer(s): Kimberly Lehrfeld, Pharm.D., Risk Management Analyst
Division of Risk Management
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Drug Name(s): Adasuve (loxapine *Staccato* inhalation powder)

Therapeutic Class: Antipsychotic

Dosage and Route: 5mg and 10mg single dose inhaler

Application Type/Number: NDA 22-549

Applicant: Alexza Pharmaceuticals, Inc.

*** This document contains proprietary and confidential information that should not be released to the public. ***

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review is provided in response to a request by Division of Psychiatric Products (DPP) to review and comment on Alexza Pharmaceutical, Inc.'s Risk Evaluation and Mitigation Strategy (REMS) proposal for Adasuve (NDA 22-549), originally submitted on August 4, 2011 (Seq. No. 0026) and amended on January 10, 2012 (Seq. No. 0032) and March 27, 2012 (Seq. No. 0039).

As discussed with DPP and Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), DRISK agrees that a REMS is necessary to ensure the benefits of Adasuve outweigh the potential risk of negative outcomes associated with Adasuve-induced bronchospasm in patients with agitation associated with schizophrenia or bipolar I disorder in adults.

This review documents DRISK's interim conclusions and recommendations on the proposed Adasuve REMS. The REMS submitted on March 27, 2012 includes the required major elements; DRISK finds it to be generally acceptable. However, additional revisions to the REMS will be required as labeling is negotiated and/or as a result of the REMS clearance process. DRISK's final approval, along with any additional revisions, will be documented in an addendum to this review.

1 BACKGROUND

1.1 INTRODUCTION

This DRISK review is provided in response to a request by DPP to review and comment on Alexza Pharmaceutical, Inc.'s REMS proposal for Adasuve (NDA 22-549), originally submitted on August 4, 2011 (Seq. No. 0026) and amended on January 10, 2012 (Seq. No. 0032) and March 27, 2012 (Seq. No. 0039). This review documents DRISK's interim conclusions and recommendations on the proposed Adasuve REMS. Additional revisions to the REMS may be required as labeling is negotiated and/or as a result of the clearance process. DRISK's final recommendations, along with any additional revisions, will be documented in an addendum to this review.

1.2 PRODUCT DESCRIPTION

Adasuve (loxapine) inhalation powder is a drug-device combination product, consisting of the drug loxapine and a single-use *Staccato* device. Loxapine is a first generation, typical antipsychotic.

Adasuve is available as a 5- and 10-mg single-use inhaler that provides rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine. Oral inhalation through the *Staccato* device initiates the controlled, rapid heating of a thin film of excipient-free loxapine to form a thermally-generated, drug vapor. The vapor condenses into aerosol particles that are dispersed into the airstream created by the patient inhaling through the mouthpiece.

Alexza is seeking approval of Adasuve for the acute treatment of agitation associated with schizophrenia and bipolar disorder.

The recommended dose for acute agitation is 10 mg administered by oral inhalation, using a single-use inhaler. (b) (4)

1.3 REGULATORY HISTORY

Following are highlights of key regulatory actions and communications for Adasuve, following submission of the original NDA.

- **December 11, 2009:** Submission, Original NDA (Seq. No. 0000)
- **October 8, 2010:** Complete Response (CR) action taken, identifying pulmonary toxicity (bronchospasm) as the primary issue
- **December 17, 2010:** End of Review Meeting to discuss the issues raised in the CR letter, and how they should be resolved. FDA stated that it would be reasonable to propose a REMS program for the safe use of Adasuve.
- **April 29, 2011:** Type C Meeting; possible components of a REMS were discussed, including Elements to Assure Safe Use (ETASU).
- **August 4, 2011:** Amendment #1 Resubmission/Class 2 (Seq. No. 0026); submission included a REMS with the following components: Medication Guide, Communication Plan, ETASU B: Healthcare Facility (HCF) Certification, Implementation System, and timetable for submission of Assessments (see Section 3.4.1)
- **October 14, 2011: REMS Oversight Committee (ROC) meeting:** DPP and DRISK presented the review team's minimum requirements for the Adasuve REMS (see Section 3.4.2) to ROC for discussion. The committee agreed that if Adasuve was approved, ETASU would be needed. They also recommended soliciting outside stakeholder input during the development of the REMS, including considering presenting the REMS at a Drug Safety Oversight Board (DSB) meeting.
- **November 16, 2011: Drug Safety Oversight Board (DSB) meeting:** FDA's proposed minimum requirements for the ADASUVE REMS were presented to the DSB, who were asked to comment on the impact the REMS might have on their respective healthcare facilities. Discussion at the DSB meeting did not result in revisions to the FDA's proposed REMS.
- **December 12, 2011: Psychopharmacologic Drugs Advisory Committee (PDAC) meeting** (supplemented with members from the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee) to discuss the efficacy and safety concerns expressed by DPP and DPARP, and the approvability of Adasuve. At this meeting, the FDA presented their concerns with Alexza's proposed REMS and the FDA's recommendations for the minimum REMS requirements. The Advisory Committee members voted

9 to 8 with 1 abstention to approve the drug with the FDA-recommended REMS and limiting administration of Adasuve to one dose in 24 hours.

- **January 10, 2012:** Submission, REMS Amendment #2 (Seq. No. 0030); REMS revised to align with the FDA-recommended REMS, as presented at the December 2011 PDAC meeting.
- **January 19, 2012:** Alexza informed of 3-month review extension, due to unsolicited major amendment.
- **February 15, 2012:** FDA Interim Comments, Set #1 [via email]. Included REMS document which had been preliminarily cleared by ORP and OCC.
- **February 22, 2012:** Submission, REMS Amendment #3; response to Interim Comment Set #1 (Seq. No. 0036)
- **March 1, 2012:** Teleconference with Alexza. Discussion of Alexza's response to Interim Comment Set #1; FDA clarified that "immediate access onsite to advanced airway management abilities" meant that these capabilities must be available within the HCF as opposed to available by calling emergency response services. The proposed post-marketing requirement study was also discussed.
- **March 1, 2012:** FDA Interim Comments, Set #2 [via email]
- **March 8, 2012:** Submission, REMS Amendment #4; Response to Interim Comment, Set #2 (Seq. No. 0038); accepted all revisions proposed by FDA in Interim Comment Set #2
- **March 16, 2012:** FDA Interim Comments, Set #3 [via email]
- **March 27, 2012:** Submission, REMS Amendment #5; Response to Interim Comment, Set #3 (Seq. No. 0039)

Upcoming Milestone:

- **April 5, 2012:** REMS Oversight Committee (ROC) meeting
- **May 4, 2012:** PDUFA date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials were reviewed:

- Proposed REMS and Supporting Document, received August 4, 2011 (Seq. No. 0026)
- Proposed REMS and Supporting Document, received January 10, 2012 (Seq. No. 0030)
- Proposed REMS, received February 22, 2012 (Seq. No. 0036)
- Proposed REMS, received March 27, 2012 (Seq. No. 39)

The following materials were referenced:

- Adasuve Prescribing Information [substantially complete labeling], dated March 12, 2012
- Clinical Review of Adasuve. Reviewer: Francis E. Becker, dated September 17, 2010.
- Pulmonary Safety Review Consult. Reviewers: A. Harry, T Michele, S. Seymour, B Choudhury, dated August 25, 2010.

2.2 ANALYSIS TECHNIQUES

The REMS proposal was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and responsiveness to Agency comments.

3 RESULTS OF REVIEW OF PROPOSED ADASUVE RISK EVALUATION AND MITIGATION STRATEGY

3.1 RISK BENEFIT CHARACTERIZATION

3.1.1 Current Therapies

- FDA-approved treatment for acute agitation (parenteral (IM) antipsychotics):¹
- Approved for acute agitation in schizophrenia and bipolar patients:
 - Aripiprazole (Abilify)
 - Ziprasidone (Geodon)
 - Approved for acute agitation in schizophrenia:
 - Olanzapine (Zyprexa)
- Other treatment for acute agitation:
- Benzodiazepines (oral or parenteral) are commonly used
 - Parenteral first generation antipsychotics

3.1.2 Severity of Risk

3.1.2.1 *Risk in context of drugs in class, among other drugs used to treat disease, prescribers familiarity with risk, monitoring and management*

The second generation IM antipsychotics and Adasuve share a similar adverse event profile, with the exception of the pulmonary adverse events associated with Adasuve.

Adasuve is the first *Staccato* product, as well as the first inhaled, psychiatric medication. Therefore, psychiatrists and Emergency Department (ED) physicians may be unfamiliar with the risks of bronchospasm associated with this inhaled product

¹ Abilify and Geodon are approved for “acute treatment of agitation.” Zyprexa is approved for “treatment of acute agitation.” The proposed indication for Adasuve is for “acute treatment of agitation.”

Current monitoring practice for agitated patients in an ED is unlikely to detect pulmonary adverse events related to Adasuve treatment. First, monitoring for pulmonary adverse events is not standard of care after treating agitated patients in ED settings. Although there is a general practice of observing agitated patients after treatment, the protocols vary between hospitals and often depend on the baseline level of agitation of the patient. Further, the hospital staff assigned to monitor these patients may not have the required medical training (e.g. security guards).

3.1.2.2 How is the risk managed across other products and/or diseases

There are no other products with a risk of bronchospasm that have required a REMS. For an overview of the drugs that are associated with anaphylaxis or immediate post-injection reactions for which FDA considered and/or required a REMS to address the risk, see Appendix A.

3.1.2.3 Seriousness of Disease

Agitation is a severe, disruptive complication of schizophrenia and mania. It may progress in minutes, hours, or days from inner distress (nervous, restless, and panic) to an outwardly apparent dysfunctional state (cursing, hostility, difficulty controlling impulses, uncooperative behavior, and increased potential for violence). When patients present in an acutely agitated state, it may require hours to days of treatment to reduce agitation symptoms while their underlying disease state is being stabilized.

3.1.3 Expected Benefit

Adasuve confers expected benefit to acutely agitated patients as a non-invasive anti-anxiety agent with a novel mechanism of administration (inhalation).

Adasuve is effective in controlling agitation. In two randomized, double-blind, placebo-controlled trials investigating 1 to 3 doses of Staccato loxapine in agitated patients with schizophrenia (Trial 004-301) or bipolar disorder (Trial 004-302), both the 5- and 10-mg doses met the primary efficacy endpoint: change in Positive and Negative Symptom Scale, Excited Component [PEC] score from baseline to 2 hours after Dose 1, active vs. placebo. In addition, both the 5- and 10-mg doses met the key secondary endpoints: Clinical Global Impression – Improvement Scale [CGI-I] score 2 hours after Dose 1, active vs. placebo.

Adasuve provides a non-invasive method of treatment for agitation. Currently the other approved treatments available for treatment of agitation are the second generation antipsychotics, which are administered intramuscularly, and oral benzodiazepines. Therefore, Adasuve may be a preferred treatment for patients since it is non-invasive.

Adasuve shows a trend toward a rapid onset of therapeutic effect. In the two pivotal studies, the treatment effect on agitation signs and symptoms, as measured by the change from baseline in the total PEC score and the 5 individual items on the PEC, was evident after the first dose and was sustained at all assessment times through the post treatment evaluation period (10 minutes up to 24 hours) for both doses of Staccato Loxapine. There are no head-to-head studies comparing Adasuve to other agents used for the acute treatment of agitation.

3.1.4 Expected Duration of Treatment

Because agitation associated with schizophrenia and bipolar disorder is an acute and intermittent condition, it is anticipated that patients will be treated with Adasuve on an infrequent basis. Per labeling and REMS requirements, patients would be limited to receiving one inhalation (b) (4) 10 mg) once within a 24 hour period.

3.2 OVERVIEW OF CLINICAL PROGRAM

Controlled Studies in Agitated Patients

Alexza completed two randomized, double-blind, placebo-controlled trials investigating 1 to 3 doses of Adasuve in agitated patients with schizophrenia (Trial 004-301) or bipolar disorder (Trial 004-302); both the 5- and 10-mg doses met the primary efficacy endpoint: change in Positive and Negative Symptom Scale, Excited Component [PEC] score from baseline to 2 hours after Dose 1, active vs. placebo. In addition, both the 5- and 10-mg doses met the key secondary endpoints: Clinical Global Impression – Improvement Scale [CGI-I] score 2 hours after Dose 1, active vs. placebo.

There were 4 patients (7.6%) with airway related adverse events in the combined Adasuve groups, compared to none in the placebo group. Two patients in the Adasuve 5 mg dose group had wheezing and one patient in the Adasuve 10 mg group had cough, all of which resolved without treatment. One patient in the Adasuve 10 mg group was discontinued from the trial due to bronchospasm. This was a 59 year old female with schizophrenia who developed labored breathing and wheezing audible without a stethoscope approximately 5 minutes after her first dose of Adasuve. She did not complain of shortness of breath. She responded to albuterol metered-dose inhaler (MDI) and oxygen via nasal cannula. Of note, this patient did not have any history of pulmonary disease.

Pulmonary Safety Studies in Patients with Asthma and COPD

In the dedicated pulmonary safety studies, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms, often requiring rescue treatment with bronchodilator medication. In the pulmonary safety study of patients with asthma, 11% of patients receiving staccato placebo and 53% of patients receiving Adasuve, required rescue treatment with a bronchodilator. In the pulmonary safety study of patients with COPD, 4% of patients receiving staccato placebo and 23% of patients receiving ADASUVE, required rescue treatment with albuterol. In both studies, there were fewer patients that received a second dose of Adasuve, because a patient was excluded from receiving a second dose if they required rescue treatment or experienced decreases in FEV1 after the first dose.

In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV1 of >10%. 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%. 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 and respiratory 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.

Pulmonary toxicity was dose-related in the safety studies. Asthma patients treated with a second dose of loxapine inhalation powder, 10 hours after the first dose, 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, because they developed a decrease in FEV1 and/or they required rescue treatment of respiratory signs and symptoms.

3.3 SAFETY CONCERNS

3.3.1 Overall Safety

In the pivotal trials (patients with schizophrenia or bipolar disorder), the most common adverse reactions were dysgeusia, sedation, fatigue, and throat irritation. Although sedation alone is not a serious side effect, it can potentially impact a healthcare practitioner's ability to monitor for, and detect bronchospasm in patients after Adasuve administration.

In the pivotal trials, patients with clinically significant pulmonary disease were excluded; however, one patient (0.2%) was discontinued from the study due to bronchospasm (required albuterol rescue and oxygen) and two patients (0.4%) developed wheezing.

3.3.2 Bronchospasm

There is a significant risk of post-inhalation bronchospasm following administration of Adasuve. The risk is higher in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD, but can occur in patients with no history of pulmonary disease.

The severity of obstruction is greater following a second dose and does not return to baseline for 24 hours or more following repeat dosing.

3.3.3 Risks associated with multiple doses of Adasuve in 24 hours

The pulmonary safety profile of Adasuve, if dosed as proposed by Alexza, is unknown. Alexza proposed allowing up to 3 doses of Adasuve, dosed 2 hours apart, in a 24 hour period. In pulmonary safety studies in healthy adults, asthma patients and COPD patients, dosing of Adasuve was given 10 hours apart. The results in these studies showed that FEV1 never returned to baseline levels 24 hours after the second dose. Additionally, there were no FEV1 measurements after the 24 hour point. Furthermore, there was limited experience in the pivotal trials with dosing Adasuve multiple times and even fewer where it was dosed at the proposed 2 hours intervals.

Concerns about the increased pulmonary adverse events seen after the second dose were raised at the December 12, 2011 Psychopharmacologic Drugs Advisory Committee (PDAC) meeting. In response, the FDA's question for the committee was changed at the meeting to ask if the committee members would vote to approve this product if the dose of Adasuve was limited to one dose in 24 hours and the FDA's recommended REMS was enacted. The committee voted 9 to 8 with one abstention for approval with these qualifiers.

3.4 PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

Following are an overview of Alexza's original REMS proposal (August 4, 2011; Seq. No. 0026), an overview of FDA's Minimum REMS Requirements, and a detailed description of Alexza's currently proposed REMS (March 27, 2012; Seq. No. 0039).

3.4.1 Overview of Sponsor's Original REMS Proposal (August 4, 2011)

Alexza's original REMS proposal included a Medication Guide, Communication Plan, ETASU, implementation system, and a timetable for submission of assessments.

The proposed Communication Plan included a Dear Healthcare Provider (DHCP) Letter, Prescriber Brochure, voluntary Education Program, and voluntary Safe Use Checklist. The safe use conditions outlined in the Safe Use Checklist were as follows:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

3.4.2 Overview of FDA's Minimum REMS Requirements

DPP, DPARP, and DRISK agreed that the REMS proposed by Alexza in August 2011, was not adequate to ensure the safe use of Adasuve, and agreed on the minimum REMS requirements described below. These requirements were presented to the ROC (October 14, 2011), the DSB (November 17, 2011), and the PDAC (December 12, 2011).

The Agency's proposed REMS also includes ETASU B- HCF certification with the Communication Plan components integrated into the ETASU requirements. However, the attestations under ETASU B for HCF certification were more comprehensive than those proposed by Alexza. First, instead of attesting to having short acting beta agonist MDI on-site, the HCF would have to attest to having immediate access on-site to advanced airway management abilities including the ability to intubate a patient, thereby, significantly limiting the HCFs that would be eligible for enrollment.

In addition, the steps for safe use that Alexza proposed in the (b) (4) *Safe Use Checklist* (i.e. screening, observing, and monitoring) are enhanced, and mandatory as part of the policies, procedures or order sets at certified HCFs. The mandatory screening and monitoring requirements must include not only visual assessments but also a physical exam with chest auscultation to detect underlying pulmonary disease and early bronchospasm, should it occur. Finally, Alexza's proposed (b) (4) *ADASUVE Education Program* would become mandatory training for certified HCF practitioners involved in prescribing, dispensing, and administering Adasuve, as well as for the HCF practitioners monitoring patients after treatment. This training would be the responsibility of the HCF representative to ensure and document.

The Agency's proposal does not include the MG as an element of the REMS.

3.4.3 Sponsor's Proposed REMS (as of March 27, 2012)



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4 DISCUSSION

REMS are intended to ensure that the benefits of the drug outweigh the risks of the drug. They are also intended to meet specific risk mitigation goals for a product that requires strategies beyond professional labeling to ensure safe use in the postmarketing setting. It is important to determine if such additional measures are feasible, appropriate, effective, and necessary to mitigate the risks.

DPP, DPARP and DRISK are in agreement that a REMS is necessary to ensure the benefits of Adasuve outweigh the potential risk of negative outcomes associated with Adasuve-induced bronchospasm in patients with agitation associated with schizophrenia or bipolar I disorder in adults.

Following is a discussion of FDA's concerns with the Sponsor's original REMS proposal, and the rationale for the currently proposed REMS.

4.1 CONCERNS WITH SPONSOR’S ORIGINAL REMS PROPOSAL:

4.1.1 Screening Requirements

Patients with active or a history of pulmonary disease (e.g. asthma or COPD) are at an increased risk for Adasuve-induced bronchospasm, and must not receive Adasuve.

Alexza’s proposed screening, which included (b) (4)

[Redacted]

is not adequate for the following reasons:

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]

Given the challenges assessing a patient’s current and past pulmonary diagnosis, screening must also include a physical exam that includes chest auscultation.

Therefore, to mitigate the risk of inappropriate patients receiving Adasuve, screening must include obtaining a patient-reported medical history and reviewing any available medical records for current medications to treat pulmonary disease and a past history of pulmonary disease. In addition, a physical exam that includes chest auscultation must be performed.

4.1.2 Monitoring Requirements

Even with the above screening, it is expected some patient will develop bronchospasm. Because of the screening challenges described above, it is expected that not all patients that are not appropriate candidates for Adasuve treatment will be identified, resulting in higher risk patients receiving Adasuve. Furthermore, in the controlled trials in agitated patients in which patients were screened for a history of pulmonary disease or active airway disease, one patient with no history of pulmonary disease had clinically significant bronchospasm.

It is important to identify bronchospasm quickly, before it progresses. Alexza proposed monitoring patients (b) (4)

[Redacted] This approach has several limitations. (b) (4)

(b) (4) Therefore, more objective measures are needed. Since monitoring FEV1 measurements is not practical in clinical practice, other monitoring parameters are needed.

To mitigate the risk of bronchospasm progressing without being detected, monitoring vital signs, including chest auscultation, every 15 minutes for a minimum of one hour is needed.

4.1.3 Management of Adasuve-Induced Bronchospasm

Having access only to a short acting bronchodilator metered dose inhaler (MDI) to treat all bronchospasm is not adequate to ensure safe use of Adasuve. First, not all patients will be able to use an albuterol MDI. If a patient has no experience using MDI's, it will be difficult to teach agitated or sedated patients proper use. Therefore, a nebulizer must be available at the certified HCF.

It is possible that, in a percentage of treated agitated schizophrenic and bipolar patients, bronchospasm will progress, undetected, to the point where albuterol will not effectively manage it. In addition, it is possible that bronchospasm, at first presentation, may be moderate or severe and a MDI is not the recommended treatment for this level of bronchospasm (per National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma). Therefore, access to advanced airway interventions will be needed to effectively manage bronchospasm that is not recognized and progresses.

Given the risk of severe patient outcomes, it is critical that appropriate treatment, for all levels of bronchospasm (i.e. mild or moderate to severe as rated by NHILA), is immediately available. Therefore, on-site access to nebulized albuterol and advanced airway interventions is required.

4.1.4 Controls to Ensure Adherence to Safe Use Conditions for Adasuve

Current monitoring practice for agitated patients in an Emergency Department (ED) is unlikely to detect pulmonary adverse events related to Adasuve treatment. Monitoring for pulmonary adverse events is not standard of care after treating agitated patients in ED settings. Although there is a general practice of observing agitated patients after treatment, the protocols vary between hospitals and often depend on the baseline level of agitation of the patient.

Since there are no other approved or commonly used treatments for acute agitation that have bronchospasm or any other pulmonary adverse event as a serious or common side effect, routine screening for active pulmonary disease or a history of pulmonary disease is not standard practice.

Therefore, requiring HCF's to have protocols, policies, and order sets in place to help ensure compliance with REMS requirements, will be a mandatory component of the ADASUVE REMS program.

4.2 DISCUSSION OF REMS TOOLS:

Adasuve Medication Guide:

DRISK recommends the medication guide be removed from the REMS. First, the intended patient population of acutely agitated patients may not be capable of reading or understanding the information due to their level of agitation. In addition, the medication guide will not help them make an informed decision about whether to take Adasuve.

Steps for Safe Use of Adasuve (previously titled Safe Use Checklist) and Order Set/Protocol Template:

The *Safe Use Checklist* was changed to a document titled *Steps for the Safe Use of Adasuve*, which can potentially be handed out or posted in appropriate treatment locations for healthcare professionals to reference during administration of Adasuve. In addition, DRISK recommends making the components of the *Steps for Safe Use of ADASUVE* mandatory under the Element to Assure Safe Use as noted above. The healthcare facility representative will have to assure that prior to ordering Adasuve the healthcare facility will have policies, procedures and/or order sets (e.g., components of the Steps for Safe Use of Adasuve) in place to assure the proper screening and monitoring of patients who will receive Adasuve. To facilitate development of these policies, the ADASUVE REMS includes an *Order Set/Protocol Template*. This document includes all screening and monitoring required by the ADASUVE REMS.

ADASUVE REMS Education Program

In order to assure healthcare facility staff is educated about the ADASUVE REMS program requirements and how to use Adasuve safely, education is mandatory under ETASU B.

Dear Healthcare Professional Letter

In order to inform psychiatrists and emergency medicine health care practitioners about the risk of bronchospasm associated with Adasuve and the ADASUVE REMS program, *Dear Healthcare Professional Letters* will be distributed at least 2 weeks prior to product launch and in the event of any substantial safety update.

5 CONCLUSION

Given the risks of post-inhalation bronchospasm following administration of Adasuve, DRISK agrees that a REMS with ETASU is needed to ensure that the benefits of Adasuve outweigh the risks. The proposed Adasuve REMS includes healthcare facility certification, an implementation system, and timetable for submission of assessments. The REMS is intended to limit administration of Adasuve in patients at highest risk of bronchospasm, help ensure patients are adequately monitored following Adasuve administration so that developing bronchospasm can be treated early, and limit dispensing of Adasuve to healthcare facilities that are able to provide immediate on-site access to advanced airway management capabilities for bronchospasm that is missed and progresses.

In conclusion, the appended REMS for Adasuve submitted on March 27, 2012, contains all revisions to the REMS that have been communicated to date. Revisions to the Supporting Document and Information Needed for Assessments are pending. Additional revisions to the REMS will be required as labeling is negotiated and/or as a result of the clearance process. DRISK's final recommendations, along with any additional revisions, will be documented in an addendum to this review.

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/s/

MEGAN M MONCUR
04/02/2012

CLAUDIA B MANZO
04/02/2012
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance

REMS Memorandum

TO: Thomas P. Laughren, MD., Director
Division of Psychiatry Products

THROUGH: Tamika White, Acting Branch Chief
Post Marketing Safety Branch
Division of Safety Compliance
Office of Compliance (OC)

FROM: Kendra Biddick, Consumer Safety Officer
Post Marketing Safety Branch, REMS Compliance Team
Division of Safety Compliance
Office of Compliance (OC)

SUBJECT: Risk Evaluation and Mitigation Strategy (REMS) Review

NDA 022549

This memorandum serves as the OC review of the Adasuve (loxapine) inhalation powder (NDA 022549) REMS submitted by Alexza Pharmaceuticals, Inc. to the Food and Drug Administration (FDA) on January 10, 2012, and revised by the Office of Surveillance and Epidemiology on February 16, 2012.

BACKGROUND

Loxapine is a first generation, typical antipsychotic. Loxapine inhalation powder is formulated as a single-dose, inhaled powder which is vaporized and delivered via the Staccato device. Alexza Pharmaceuticals is seeking approval of loxapine inhalation powder for the acute treatment of agitation associated with schizophrenia and bipolar disorder.

Loxapine inhalation powder via the Staccato device provides a non-invasive method of treatment for agitation, but is associated with a serious pulmonary adverse event. The primary safety issue is the risk of acute bronchospasm. This risk is increased in patients with underlying airway hyper responsiveness, including asthma and chronic obstructive pulmonary disease (COPD).

In meetings between the Division of Psychiatry Products (DPP), Office of Surveillance and Epidemiology, and OC, DPP has been very clear that in order to prevent deaths, healthcare facilities must have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation.

March 30, 2012

On February 16, 2012, FDA sent an email to Alexza Pharmaceuticals which included a REMS document that DRISK had drafted. This review provides Compliance's comments on the February 16, 2012 REMS document. The purpose of these comments is to improve the enforceability of the Adasuve REMS document.

OC OBSERVATIONS ON THE ADASUVE REMS DOCUMENT (bold italics added to highlight points of interest)

(b) (4)



OC RECOMMENDATIONS

Recommendations to Alexza via the Office of Surveillance and Epidemiology (OSE) and the Division of Psychiatry Products (DPP) should include the following modifications to the REMS document. OC's changes are underlined.

1. Modify Section II.A.1.f to read as follows:

Each health care facility must train relevant staff (e.g., staff involved in prescribing, dispensing or administering ADASUVE and monitoring patients after ADASUVE administration) on the safe use of ADASUVE, as described in the ADASUVE REMS Education Program. This training must be documented and is subject to audit.

2. Modify section II.A.1.j to read as follows:

Each health care facility must establish procedures, protocols and/or order sets to help ensure compliance with the safe use conditions required in the ADASUVE REMS, and

as described II.A.1.b through i., above. These procedures, protocols and/or order sets must be documented and are subject to audit.

3. Modify section II. A.1.k.iii to read as follows:

The health care facility will meet the requirements in b. through j. above prior to certification.

4. Modify Section 2.B.1.1.i. to read as follows:

The Wholesaler/Distributor will ensure that relevant staff are adequately trained on the Adasuve REMS program procedures and will follow the requirements of the Adasuve REMS program. This training must be documented and is subject to audit.

Recommendations to OSE and DPP for the approval letter.

The approval letter should include the following items in the assessment plan.

For the initial assessment only:

1. The dates REMS materials became available to health care facilities both on the two websites mentioned in the REMS and by calling the call center.
2. The dates health care facility and wholesaler/distributor enrollment could successfully be completed online, by mail, and by fax.
3. The dates the Adasuve REMs education program became available as an in-service, and online.

For the current period and cumulatively:





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/s/

KENDRA A BIDDICK
03/30/2012

TAMIKA T WHITE
03/30/2012