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RESEARCH**

APPLICATION NUMBER:
022549Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	December 10, 2012
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review Memo
NDA	22549
Sponsor	Alexza Pharmaceuticals
Type of Submission	Complete Response
Submission Date	June 21, 2012
Related IND	73248
Cross-referenced NDAs	17-525, 17-658, and 18-039 (Lederle Labs) Loxapine oral tablets, loxapine oral solution, and loxapine intramuscular injection
Proprietary / Established (USAN) names	ADASUVE [®] <i>Staccato</i> [®] Loxapine for oral Inhalation
Therapeutic Class	Antipsychotic
Dosage forms / strength	Combination Drug-Device Product – Single Use Inhalation Device Loxapine 10 mg
Proposed Indications	1. Acute Agitation associated with Schizophrenia 2. Acute Agitation associated with Bipolar Disorder, Mania
Recommended:	Approval

1. Introduction to the Review

This is the third review cycle for the NDA. I have filed two previous Cross-Discipline Team Leader review memos (October 5, 2010 and April 25, 2012). This memo will focus on the CMC deficiencies that prompted the Complete Response action in the previous review cycle (May 2, 2012). In the current complete response submission, the sponsor has provided new CMC information. The CMC team, the CDRH Office of Compliance, and the CDER Office of Compliance reviewed this new information. There were no new clinical data to review. This review will also discuss the finalized Adasuve REMS and the label for Adasuve. The CMC reviewers and the CDRH and CDER Office of Compliance have concluded that the sponsor has resolved the CMC deficiencies. The review teams from all other disciplines have concluded that there are no outstanding issues for the NDA, and they support approval of the application. I agree with all reviewers, and I recommend approval of the application.

2. Background and Regulatory History

On December 11, 2009 Alexza Pharmaceuticals submitted NDA 22-549 for Adasuve (*Staccato*[®] loxapine for oral inhalation) in the treatment of agitation associated with

schizophrenia or bipolar disorder. This is a 505(b)(2) marketing application, referencing the innovator drug product, Loxitane (loxapine oral tablets, oral solution, and intramuscular injection; Lederle Labs; NDAs 17-525, 17-658, and 18-039, respectively). Loxapine is a first generation (typical) antipsychotic drug that was approved in 1975 for the treatment of schizophrenia. Loxapine is a dibenzoxazepine compound. It binds with high affinity to the dopamine D₂ receptor and acts as an antagonist at this receptor. Loxapine also binds at the serotonin 5-HT_{2a} receptor. Although no longer marketed, an intramuscular formulation of loxapine had been available for the treatment of acute agitation. *Staccato* Loxapine is a new dosage form of loxapine. *Staccato* Loxapine is based on the proprietary *Staccato* delivery system developed by Alexza Pharmaceuticals, Inc. (Alexza). *Staccato*[®] Loxapine for oral Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery of loxapine through absorption at the deep lung. Oral inhalation through the device initiates the controlled, rapid heating (up to 400°C) of a thin film of excipient-free loxapine, resulting in a thermally generated drug vapor, which rapidly condenses into aerosol particles. The particles are of an appropriate size for delivery to the deep lung where the drug is rapidly absorbed.

2.1 First Review Cycle

In the first review cycle, the Division concluded that the sponsor had demonstrated the efficacy of Adasuve in the treatment of acute agitation associated with schizophrenia or bipolar disorder. There were two pivotal trials that essentially had the identical study design. Study AMDC-004-301 included 344 adult subjects with schizophrenia; Study AMDC-004-302 included 314 adult subjects with bipolar disorder. These were randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trials of loxapine 5 mg or 10 mg. The primary endpoint was the Positive and Negative Syndrome Scale-Excited Component Scale (PEC). The PEC is a valid and reliable measure of acute agitation in these populations. The primary endpoint was the change in PEC score at 2 hours after dosing. In both studies and for both doses, loxapine was superior to placebo. The differences in treatment effects were statistically and clinically significant; there was substantial reduction in the severity of agitation. Moreover, the treatment effects were apparent at all time points assessed, beginning at 10 minutes after dosing (the first assessment time point).

However, the Division took a Complete Response action on 8 October 2010, because of the risk of bronchospasm and related serious outcomes. We concluded that the initially proposed labeling would not adequately mitigate the risk of pulmonary toxicity. Furthermore, the sponsor had not submitted a Risk Evaluation Mitigation Strategy (REMS) for mitigating the risks. In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 (up to 20%) for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. Furthermore, standard bronchoprovocation tests induce a decrease in FEV1 of 10-20%. In subjects with asthma or COPD, the FEV1 findings were marked. Moreover, a substantial proportion of subjects in the asthma and COPD studies had significant respiratory signs and symptoms requiring rescue treatment with bronchodilator

medication. 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. A high proportion (40-69%) of asthmatic and COPD subjects had significant respiratory adverse reactions, and a substantial proportion required rescue treatment with bronchodilator medication. Respiratory adverse reactions included bronchospasm, dyspnea, wheezing, chest discomfort and tightness, throat tightness, and cough.

Pulmonary toxicity was dose-related. Subjects treated with a second dose had greater decreases in FEV1 (compared to their first dose) which did not return to baseline at 32 hours post-dose. A significant proportion of asthmatic and COPD subjects were discontinued from the study before receiving the planned second dose, because they had a decreased FEV1 and/or the need for rescue treatment. As a result, one could not determine the true nadir of the FEV1 following treatment with inhaled loxapine.

Additional factors could contribute to an excessive risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. Another concern was that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Moreover, sedation from loxapine could obscure respiratory signs and symptoms.

2.2 Second Review Cycle

On 4 August 2011, the sponsor submitted a Class 2 Complete Response. The contents of the submission included a REMS with Elements to Assure Safe Use and revised product labeling. The sponsor submitted new data from human factors and usability studies. The sponsor also submitted a protocol for a postmarketing observational study to assess the risk of bronchospasm when used in clinical practice under the Adasuve REMS. There were no new clinical efficacy or safety data in the submission. During the review cycle, the Agency developed a version of the Adasuve REMS, based on the sponsor's proposed REMS. We also developed a revised version of labeling.

On 12 December 2011, we held a Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting to discuss the application. The main topics of discussion included: the serious pulmonary safety concerns associated with Adasuve, the risk/benefit profile of the product, whether the risks could be adequately mitigated or managed with a REMS, whether there are unique benefits of Adasuve treatment compared to other available treatments, and whether the sponsor should be required to conduct a large observational study as a premarketing or a postmarketing requirement. The committee was supplemented with members from the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The committee members' views on the risk/benefit profile were divided; however, the committee voted

9 to 8 (with one abstention) to approve the application with the FDA-developed REMS and limiting Adasuve administration to one dose within a 24-hour period.

The Agency did not approve the application, because there were critical CMC deficiencies observed during inspection of Alexza's Mountain View, California manufacturing facility. The sponsor had not responded adequately to the concerns outlined by the CDRH Office of Compliance; several of these were repeat observations. There were deficiencies in the device validation processes. (b) (4)

In addition, the sponsor had failed to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA). The Division issued a Complete Response letter on May 2, 2012. A General Advice letter formally conveyed the inspectional deficiencies (June 7, 2012).

2.3 Third Review Cycle

On 21 June 2012, the sponsor submitted the second Complete Response to address the CMC deficiencies outlined by the Agency in the Complete Response letter and the General Advice letter. (b) (4)

. During this cycle, the CDRH Office of Compliance District Office performed another inspection of the Alexza manufacturing facility. The Agency finalized the Adasuve REMS and labeling.

2.4 Foreign Regulatory History and Actions

In October 2011, Alexza submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) via the Centralized Procedure in the European Union. The application had been under EMA review as of May 2012. The target submission date for the responses had been July 2012. We will request that Alexza provide an update on the foreign regulatory history.

During the second review cycle, Alexza provided the Division with the EMA's preliminary list of questions (Day 120 LOQ) for the sponsor. EMA had identified several principal deficiencies and concerns. The principal issues are summarized below:

Clinical: (b) (4)

[Redacted content]

Safety:

(b) (4)

Risk Management Plan:

(b) (4)

Quality (CMC):

(b) (4)

3. Chemistry Manufacture and Controls (CMC) Review – David Claffey, Ph.D.

David Claffey Ph.D. performed the CMC review. Dr. Claffey has previously filed reviews for the NDA (5/21/10, 9/10/10, 10/5/10, 11/15/11, 4/23/12, 8/6/12, and 12/5/12).

The process validation on the 10 mg dose has been successfully completed, and the final report was submitted to the Office of Compliance and the San Francisco District Office.

(b) (4)

(b) (4)

(b) (4)

(b) (4)
The results from process validation on the 10 mg dose demonstrate that the (b) (4) results were well within acceptance criteria, and a high degree of process capability was observed.

(b) (4)

(b) (4)
r. Claffey agrees that no equivalent issues were detected in the process validation 10 mg strength. (b) (4)

(b) (4)
Thus, the Agency requested that the sponsor provide a justification about why this should not be of concern for the 10-mg strength.

(b) (4)
Dr. Claffey concluded that the sponsor has presented a reasonable but not absolutely definitive explanation for the deviation and justification why this issue would not impact the quality of the 10 mg strength product. (b) (4)

(b) (4)
Dr. Claffey stated that, given the novelty of this product and the complex factors that impact particle size, the sponsor appears to have offered a reasonable explanation for these deviations and why they will not impact the 10 mg strength product. (b) (4)

Dr. Claffey has concluded that there are no unresolved CMC issues, and he recommends approval of the application. I agree with Dr. Claffey's conclusions and recommendations.

4. Office of Compliance Inspection of Manufacturing Facilities

The Complete Response Letter (May 2, 2012) and the General Advice Letter (June 7, 201) summarized the CMC deficiencies. There were critical CMC deficiencies observed during inspection of Alexza's Mountain View, California manufacturing facility. The sponsor had not responded adequately to the concerns outlined by the CDRH Office of Compliance; several of these were repeat observations. There were deficiencies in the device validation processes. (b) (4)

A number of production and manufacturing processes had not been validated under proposed commercial batch conditions (Product Performance Qualification). In addition, the sponsor had failed to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA).

During this review cycle, the Office of Compliance reviewed the sponsor's submission, and the CDRH San Francisco District Office conducted a repeat inspection of the Alexza manufacturing facility in Mountain View, California. OC filed the Establishment Evaluation Request Summary Report (EES) on November 29, 2012. The CDER Office of Compliance provided an overall recommendation of "Acceptable," based on: 1) the District Office's inspection of the Alexza Pharmaceuticals manufacturing facilities and recommendation of Acceptable, and 2) the OC Acceptable recommendation after inspection of the API manufacturer site: (b) (4). DMF (b) (4) was acceptable.

5. Clinical

Francis Becker, M.D. performed the clinical review (November 27, 2012). Dr. Becker previously filed reviews for the NDA (9/17/10, 9/8/11, and 4/9/12). There were no new clinical efficacy or safety data to review for the current submission, and there are no outstanding clinical issues for this submission. Dr. Becker summarized the revisions to the REMS and Adasuve labeling, and he provided his overall assessment of the application. Dr. Becker recommends approval of the application. He concluded that the

sponsor clearly demonstrated the efficacy of Adasuve in the treatment of acute agitation in patients with schizophrenia or bipolar disorder. In his extensive reviews, he has discussed in detail the pulmonary toxicity associated with Adasuve. Dr. Becker acknowledges that treatment with Adasuve can cause bronchospasm and poses a risk of other serious outcomes; however, he has concluded that the Adasuve REMS and labeling can significantly mitigate the risks. He also acknowledges that it is possible that the REMS would not completely mitigate the pulmonary risks. The main components of the REMS and labeling include the following:

- Adasuve will be contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung diseases associated with bronchospasm.
- Adasuve must be administered only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation).
- Healthcare providers who would administer Adasuve must: 1) screen patients for a history of asthma, COPD, and other pulmonary disease prior to administering Adasuve; 2) examine patients (including chest auscultation) for respiratory signs (e.g., wheezing) prior to administering Adasuve; and 3) monitor patients for signs and symptoms (i.e., vital signs and chest auscultation) of bronchospasm at least every 15 minutes for a minimum of one hour following treatment with Adasuve
- The maximum dose of Adasuve is a single administration of 10 mg within a 24-hour period.
- Relevant staff from healthcare facilities and wholesalers/distributors must be adequately trained on the ADASUVE REMS program and procedures. This training must be adequately documented and subject to audit.

Dr. Becker also notes that Adasuve may have unique benefits in the treatment of acute agitation associated with schizophrenia or bipolar disorder. Adasuve is a non-invasive treatment that does not require intramuscular injection or physical restraint. As a result, there is a decreased risk of injury to patients and healthcare providers, compared to treatment with an intramuscular injection. In addition, oral administration of inhaled loxapine results in rapid delivery and absorption of loxapine in the deep lung, approaching intravenous kinetics. The studies demonstrated a rapid, significant reduction in agitation at the first time point tested (10 minutes post-dose).

Dr. Becker agrees with requiring the sponsor to conduct a large, postmarketing observational study to assess the safety of Adasuve when used in clinical practice under the Adasuve REMS and labeling. The objectives are to assess the risk of bronchospasm and related serious outcomes and to assess the performance of the REMS in mitigating the risks. Dr. Becker agrees with Dr. Parker from the Division of Epidemiology, regarding her recommendations on the sponsor's proposed protocol for the observational study.

I agree with Dr. Becker's conclusions and recommendations.

6. Division of Pulmonary and Allergy Products (DPARP)

Theresa M. Michele, M.D. performed the DPARP review (November 26, 2012). Dr. Michele and Sally Seymour, M.D. have worked closely with the Division and provided expert advice throughout the NDA review cycles. Dr. Michele has filed previous reviews for NDA 22549. The DPARP review team has assessed the pulmonary findings and risks, and they made substantial contributions to the development of the Adasuve Risk Evaluation and Mitigation Strategy and labeling for the product. During this review cycle, there were no new clinical data for Dr. Michele to review.

Dr. Michele has concluded the following:

There is a significant risk of post-inhalation bronchospasm following administration of inhaled loxapine, particularly in patients with underlying airway hyperresponsiveness caused by conditions such as asthma and COPD. The severity of obstruction is greater following a second dose and does not return to baseline for 24 hours or more following repeat dosing. Characteristics of the patient population, including a high prevalence of smoking and inability to give a reliable history, increase the risk of bronchospasm following inhaled loxapine administration. During this review cycle, DPARP recommendations regarding communication of risk and mitigation strategies are incorporated into the proposed product labeling, REMS, and PMC study. These strategies are expected to mitigate, but not eliminate, the risk of severe bronchospasm with inhaled loxapine.

I agree with Dr. Michele's conclusions and recommendations.

7. Division of Risk Management (DRISK)

Kimberly Lehrfeld, Pharm.D. performed the DRISK review (December 2012). Dr. Lehrfeld has worked extensively throughout the review cycles on developing the Agency's version of the Adasuve REMS. Her recent review is an addendum to the Division of Risk Management (DRISK) Final Risk Evaluation and Mitigation Strategy (REMS) review, filed on April 2, 2012. Her current review provides a history of the revisions of the Adasuve REMS materials since April 12, 2012 and includes the final, agreed upon Adasuve REMS document and Adasuve REMS materials.

The ADASUVE REMS with Elements to Assure Safe Use (ETASU) is intended to:

- 1) prevent administration of Adasuve to patients at highest risk of bronchospasm,
- 2) ensure that healthcare providers monitor patients adequately following use of inhaled loxapine, and
- 3) ensure that patients who develop bronchospasm are treated as early and effectively as possible.

Adasuve is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung diseases associated with bronchospasm. Adasuve must be administered only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation). Healthcare providers who would administer Adasuve must:

- 1) screen

patients for a history of asthma, COPD, and other pulmonary disease prior to administering Adasuve; 2) examine patients (including chest auscultation) for respiratory signs (e.g., wheezing) prior to administering Adasuve; and 3) actively monitor patients for signs and symptoms (i.e., vital signs and chest auscultation) of bronchospasm at least every 15 minutes for a minimum of one hour following treatment with Adasuve. The maximum dose of Adasuve is a single administration of 10 mg within a 24-hour period.

Each enrolled 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. 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 it is subject to audit. REMS materials included under the ETASU-B Healthcare Facility Certification include: 1) Dear Healthcare Professional Letter (DHCP), 2) ADASUVE REMS Education Program, 3) Steps for the Safe Use of ADASUVE, 3) Healthcare Provider Brochure, 4) Health Care Facility Information and Enrollment Form, 5) Order Set/Protocol Template, and 6) ADASUVE REMS website (www.adasuverems.com).

The Agency's REMS Oversight Committee (ROC) has reviewed the ADASUVE REMS on two separate occasions and agrees with the currently proposed plan. The sponsor has agreed to submit REMS assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. Dr. Lehrfeld has concluded that these restrictions likely will limit, but may not completely eliminate potentially severe adverse airway events that may occur with inhaled loxapine. During this review period, the risk messages and content of the Adasuve REMS did not change significantly. The focus during this cycle was to finalize the REMS Assessment and Audit (b) (4), and update all REMS materials to reflect final Adasuve Prescribing Information.

Dr. Lehrfeld has concluded that the amended REMS for Adasuve contains the appropriate and agreed upon revisions on the REMS components Healthcare Facility Certification as stipulated by the Agency. 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. I agree with Dr. Lehrfeld's conclusions and recommendations.

8. Division of Medication Error Prevention and Analysis (DMEPA)

Loretta Holmes, BSN, Pharm.D performed the DMEPA labeling review (October 12, 2012). Dr. Holmes participated in numerous labeling meetings throughout the review cycles. She filed previous DMEPA reviews (March 12, 2012 and April 9 2012). The DMEPA team reviewed the device label, pouch labeling, carton labeling, and Instructions for Use labeling, and they provided recommendations during all review cycles. The

Division has incorporated all of the DMEPA recommendations in labeling for the product. The sponsor has accepted all of the Agency's requests regarding labeling.

Dr. Holmes also performed the proprietary name review (October 5, 2012). DMEPA finds the proposed proprietary product name, Adasuve, acceptable.

9. Division of Medical Policy Programs (DMPP) Patient Labeling Team Review

The sponsor has proposed a medication guide for the product. The Division did not require a medication guide, and the medication guide is not a necessary component of the Adasuve REMS.

Shawna Hutchins, MPH, BSN, RN performed the patient labeling review (March 16, 2012). Dr. Hutchins participated in numerous labeling meetings throughout the NDA review cycles. She reviewed the full prescribing information, the Instructions for Use, and the proposed medication guide. Dr. Hutchins has provided recommendations that the Division has incorporated in the medication guide. The sponsor has accepted the Agency's revised medication guide.

10. Division of Epidemiology Review

The Division will require the sponsor to conduct a large, postmarketing, nonrandomized, observational study to assess the safety of Adasuve when used in clinical practice under the ADASUVE REMS and Adasuve labeling. The objectives are to 1) assess the risk of bronchospasm and related serious outcomes when Adasuve is used in clinical practice, and 2) assess the performance of the REMS in mitigating the risk of bronchospasm. In response to our request, the sponsor submitted a protocol for the observational study: "A Post-Marketing Observational Study to Evaluate the Safety of ADASUVE (*Staccato* loxapine for inhalation) in Agitated Patients with Schizophrenia or Bipolar Disorder" – Version 0.3, Dated 30-MAR-2012

Cary Parker, M.P.H. performed the Division of Epidemiology review (November 27, 2012). She reviewed the sponsor's proposed protocol. This will be a multicenter, non-randomized, prospective, post-marketing observational cohort study to evaluate the safety of Adasuve when used in the routine clinical setting in agitated patients with schizophrenia or bipolar disorder. The sponsor plans to enroll approximately 10,000 patients

(b) (4)

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(b) (4)

Generally, I agree with Dr. Parker's conclusions and recommendations.

11. Division of Pharmacovigilance

Ida-Lina Diak, Pharm.D. and Tracy Salaam, Pharm.D. (Division of Pharmacovigilance-1, OSE) collaborated with the Division throughout the review cycles. Dr. Diak and Dr. Salaam provided input on the REMS and the enhanced pharmacovigilance safety reporting requirements regarding bronchospasm and related serious outcomes.

12. Pediatric Use, PREA waivers or deferrals, Pediatric Plan

The use of loxapine for oral inhalation has not been studied in pediatric patients. The sponsor submitted a pediatric plan for studies in pediatric patients (b) (4)

The general study design and planned doses are reasonable. (b) (4)

Generally, the study design appears reasonable. (b) (4)

The Division presented the pediatric plan to the PeRC. The sponsor requested a partial waiver for bipolar studies in patients less than 10 years of age, because it is extremely difficult to make a diagnosis of bipolar disorder in this age group. The sponsor requested a partial waiver for schizophrenia studies (b) (4) because it is extremely difficult to make a diagnosis of schizophrenia in this age group. Thus, such studies would be impractical or impossible. The Division supported the request for the partial waiver. The sponsor requested a deferral for studies in acute agitation in pediatric patients with schizophrenia (b) (4) or bipolar disorder (≥ 10 years of age). The Division supported this request for a deferral. An efficacy study in these populations would be valuable, because the product may provide a meaningful clinical benefit compared to currently available atypical antipsychotics for intramuscular injection used to treat acute agitation. The comparative benefits could include the same as for adults; this would be a non-invasive treatment that could provide rapid control of acute agitation, with a lower risk of physical injury. Furthermore, treatment with this product would be

less likely to be perceived as being coercive. Thus the use of this option could assist in strengthening the therapeutic alliance between the patient and healthcare providers.

PeRC granted a partial waiver of schizophrenia studies in patients (b) (4) of age and a partial waiver of bipolar studies in patients less than 10 years of age. PeRC granted a deferral for schizophrenia studies in patients (b) (4) old and a deferral for bipolar studies in patients ≥ 10 years old.

The PeRC had several recommendations: 1) (b) (4); 2) the Division should request that the sponsor submit the complete efficacy and PK protocols in a PPSR; 3) the sponsor should not initiate the studies until the Agency has issued a pediatric written request; and 4) the Division should state in the written request that we would partially rely on efficacy data from the adult studies.

Reviewer's note: (b) (4)

13. Pediatric and Maternal Health Staff Consult

Erica Radden, M.D., performed the consult review for the Pediatric and Maternal Health Staff. Dr. Radden notes that this application triggered PREA, because the application is for a new indication and involves a new dosage form and route of administration of loxapine. Loxapine for inhalation has not been evaluated in pediatric patients. In accordance with the PREA, the sponsor submitted a request for a partial waiver in children under age 10 with bipolar disorder and children under the (b) (4) with schizophrenia. It is difficult to make these diagnoses in these age groups; thus, studies in these age groups are impossible or highly impractical, because the number of pediatric patients in this age group is very small (section 505B(a)(4)(B)(i) of the Act). (b) (4)

(b) (4). Dr. Radden concluded that the Agency can grant a partial waiver, because the necessary studies in these young age groups are impossible or highly impracticable. Dr. Radden also agrees that the Agency should grant a deferral for studies in schizophrenia in patients (b) (4) and in studies of bipolar I disorder in patients ≥ 10 years old. The product could provide a meaningful benefit over existing therapies.

Dr. Radden agrees with the proposed labeling in the Specific Populations – Pediatric Use section:

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

14. Advisory Committee Meeting

We did not hold an advisory committee meeting during this cycle, because the application was discussed in detail at the Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting on 12/12/11. The committee was supplemented with members from the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The committee discussed the potential risks and benefits of treatment with Adasuve, and they considered the sponsor's and the Agency's proposed REMS programs and product labeling. The Advisory Committee members voted 9 to 8 (with one abstention) to approve Adasuve with the FDA-recommended REMS and limiting administration to one dose within a 24-hour period.

15. Labeling Review

The multidisciplinary review team collaborated throughout the review cycles to develop product labeling. We reached a consensus on all aspects of labeling. The main focus of labeling is to describe and mitigate the risk of bronchospasm and related serious outcomes, consistent with the Agency's REMS. The sponsor has accepted the Division's version of Adasuve labeling.

The sections below present the language from the critical sections of labeling that address the risk of bronchospasm and mitigation of these risks. These include the Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions, and Adverse Reactions.

15.1 Boxed Warning:

WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [see Warnings and Precautions (5.1, 5.2)]. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE [see Dosage and Administration (2.2, 2.4) and Contraindications (4)].

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS [see Warnings and Precautions (5.2)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.3)].

15.2 Dosage and Administration:

2.1 DOSING INFORMATION

ADASUVE must be administered only by a healthcare professional. ADASUVE is administered by oral inhalation only. The recommended dose for acute agitation is 10 mg administered by oral inhalation, using a single-use inhaler. Administer only a single dose within a 24-hour period [see Warnings and Precautions (5.1)].

2.2 REQUIRED EXAMINATION PRIOR TO DOSING

Prior to administering ADASUVE, screen all patients for a history of asthma, COPD, or other pulmonary disease, and examine patients (including chest auscultation) for respiratory signs (e.g. wheezing) [see Warnings and Precautions (5.1)].

2.4 MONITORING TO ASSESS SAFETY

Monitor the patient for signs and symptoms of bronchospasm after ADASUVE administration. Perform a physical examination, including chest auscultation, at least every 15 minutes for at least one hour after ADASUVE administration [see Warnings and Precautions (5.1)].

15.3 Contraindications:

ADASUVE is contraindicated in patients with the following:

- Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm [see Warnings and Precautions (5.1)]
- Acute respiratory symptoms or signs (e.g., wheezing) [see Warnings and Precautions (5.1)]
- Current use of medications to treat airways disease, such as asthma or COPD [see Warnings and Precautions (5.1)]
- History of bronchospasm following ADASUVE treatment [see Warnings and Precautions (5.1)]
- Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine.

15.4 Warnings and Precautions:

5.1 BRONCHOSPASM

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest [see Adverse Reactions (6.1)]. Administer ADASUVE only in an

enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [*see Boxed Warning and Warnings and Precautions (5.2)*].

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history of asthma, COPD, and other lung disease associated with bronchospasm, acute respiratory symptoms or signs, current use of medications to treat airways disease, such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing) [*See Dosage and Administration (2.2) and Contraindications (4)*]. Monitor patients for symptoms and signs of bronchospasm (i.e., vital signs and chest auscultation) at least every 15 minutes for a minimum of one hour following treatment with ADASUVE [*see Dosage and Administration (2.4)*]. ADASUVE can cause sedation, which can mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm, as indicated by changes in forced expiratory volume in 1 second (FEV1), was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose within a 24 hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE.

5.2 ADASUVE REMS TO MITIGATE BRONCHOSPASM

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a REMS called the ADASUVE REMS. [*see Boxed Warning and Warnings and Precautions (5.1)*] Required components of the ADASUVE REMS are:

- Healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site access to equipment and personnel trained to provide advance airway management, including intubation and mechanical ventilation.
- Wholesalers and distributors that distribute ADASUVE must enroll in the program and distribute only to enrolled healthcare facilities.

Further information is available at www.adasuverems.com or 888-970-7367.

15.5 Adverse Reactions:

Airway Adverse Reactions in the 3 Trials in Acute Agitation

Agitated patients with Schizophrenia or Bipolar Disorder: In the 3 short-term (24-hour), placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar disorder (Studies 1, 2, and 3), bronchospasm (which includes reports of wheezing, shortness of breath and cough) occurred more frequently in the ADASUVE group, compared to the placebo group: 0% (0/263) in the placebo group and 0.8% (2/259) in the

ADASUVE 10 mg group. One patient with schizophrenia, without a history of pulmonary disease, had significant bronchospasm requiring rescue treatment with a bronchodilator and oxygen.

Bronchospasm and Airway Adverse Reactions in Pulmonary Safety Trials

Clinical pulmonary safety trials demonstrated that ADASUVE can cause bronchospasm as measured by FEV1, and as indicated by respiratory signs and symptoms in the trials. In addition, the trials demonstrated that patients with asthma or other pulmonary diseases, such as COPD are at increased risk of bronchospasm. The effect of ADASUVE on pulmonary function was evaluated in 3 randomized, double-blind, placebo-controlled clinical pulmonary safety trials in healthy volunteers, patients with asthma, and patients with COPD. Pulmonary function was assessed by serial FEV1 tests, and respiratory signs and symptoms were assessed. In the asthma and COPD trials, patients with respiratory symptoms or FEV1 decrease of $\geq 20\%$ were administered rescue treatment with albuterol (metered dose inhaler or nebulizer) as required. These patients were not eligible for a second dose; however, they had continued FEV1 monitoring in the trial.

Healthy Volunteers: In the healthy volunteer crossover trial, 30 subjects received 2 doses of either ADASUVE or placebo 8 hours apart, and 2 doses of the alternate treatment at least 4 days later. The results for maximum decrease in FEV1 are presented in Table 2. No subjects in this trial developed airway related adverse reactions (cough, wheezing, chest tightness, or dyspnea).

Asthma Patients: In the asthma trial, 52 patients with mild-moderate persistent asthma (with FEV1 $\geq 60\%$ of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose. Approximately 67% of these patients had a baseline FEV1 $\geq 80\%$ of predicted. The remaining patients had an FEV1 60-80% of predicted. Nine patients (17%) were former smokers. As shown in Table 2 and Figure 7, there was a marked decrease in FEV1 immediately following the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 303 mL and 9.1%, respectively). Furthermore, the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 537 mL and 14.7 %, respectively). Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat tightness, and wheezing) occurred in 54% of ADASUVE-treated patients and 12% of placebo-treated patients. There were no serious adverse events. Nine of 26 (35%) patients in the ADASUVE group, compared to one of 26 (4%) in the placebo group, did not receive a second dose of study medication, because they had a $\geq 20\%$ decrease in FEV1 or they developed respiratory symptoms after the first dose. Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 54% of patients in the ADASUVE group [7 patients (27%) after the first dose and 7 of the remaining 17 patients (41%) after the second dose] and 12% in the placebo group (1 patient after the first dose and 2 patients after the second dose).

COPD Patients: In the COPD trial, 53 patients with mild to severe COPD (with FEV1 $\geq 40\%$ of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose.

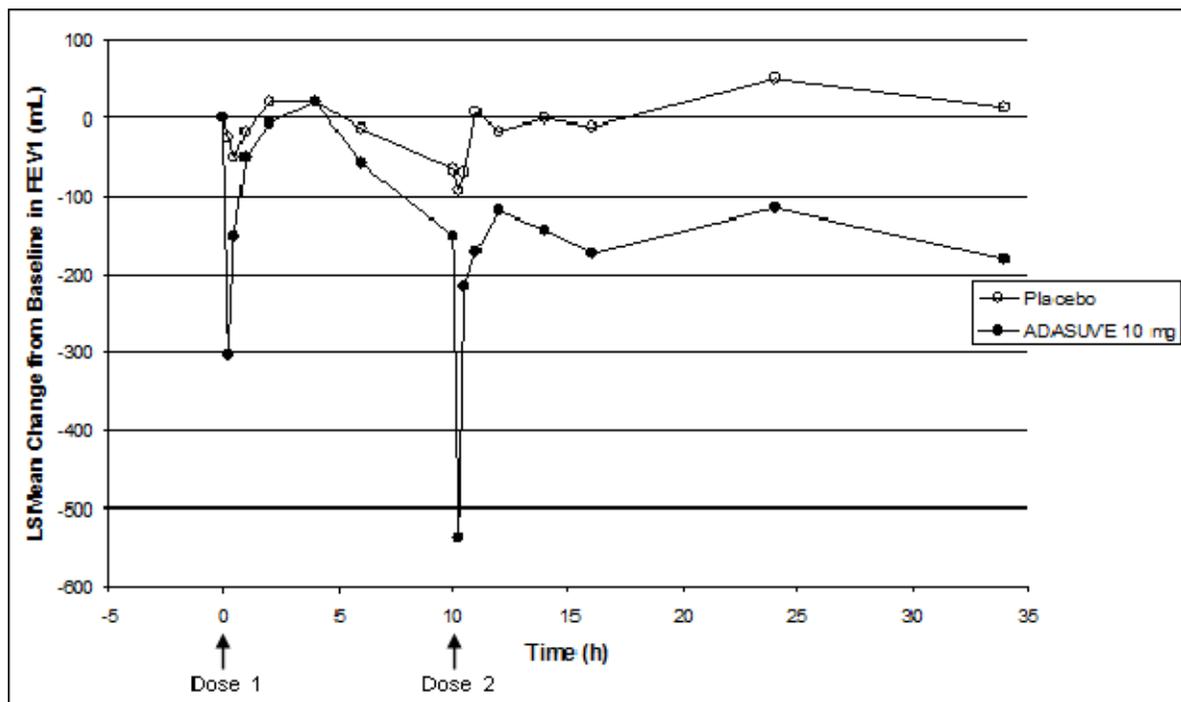
Approximately 57% of these patients had moderate COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II]; 32% had severe disease (GOLD Stage III); and 11% had mild disease (GOLD Stage I). As illustrated in Table 2 there was a decrease in FEV1 soon after the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 96 mL and 3.5%, respectively), and the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 125 mL and 4.5%, respectively). Respiratory adverse reactions occurred more frequently in the ADASUVE group (19%) than in the placebo group (11%). There were no serious adverse events. Seven of 25 (28%) patients in the ADASUVE group and 1 of 27 (4%) in the placebo group did not receive a second dose of study medication because of a $\geq 20\%$ decrease in FEV1 or the development of respiratory symptoms after the first dose. Rescue medication (albuterol via MDI or nebulizer) was administered to 23% of patients in the ADASUVE group: 8% of patients after the first dose and 21% of patients after the second dose, and to 15% of patients in the placebo group.

Table 2: Maximum Decrease in FEV1 from Baseline in the Healthy Volunteer, Asthma, and COPD Trials

Maximum % FEV ↓	Healthy Volunteer		Asthma		COPD	
	Placebo n (%)	ADASUVE 10 mg n (%)	Placebo n (%)	ADASUVE 10 mg n (%)	Placebo n (%)	ADASUVE 10 mg n (%)
After any Dose	N=26	N=26	N=26	N=26	N=27	N=25
≥10	7 (27)	7 (27)	3 (12)	22 (85)	18 (67)	20 (80)
≥15	1 (4)	5 (19)	1 (4)	16 (62)	9 (33)	14 (56)
≥20	0	1 (4)	1 (4)	11 (42)	3 (11)	10 (40)
After Dose 1	N=26	N=26	N=26	N=26	N=27	N=25
≥10	4 (15)	5 (19)	2 (8)	16 (62)	8 (30)	16 (64)
≥15	1 (4)	2 (8)	1 (4)	8 (31)	4 (15)	10 (40)
≥20	0	0	1 (4)	6 (23)	2 (7)	9 (36)
After Dose 2	N=26	N=25	N=25	N=17	N=26	N=19
≥10	5 (19)	6 (24)	3 (12)	12 (71)	15 (58)	12 (63)
≥15	0	5 (20)	1 (4)	9 (53)	6 (23)	10 (53)
≥20	0	1 (4)	1 (4)	5 (30)	1 (4)	5 (26)

FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories. Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug.

Figure 7: LS Mean Change from Baseline in FEV1 in Patients with Asthma



Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10.

16. Conclusions and Recommendations

16.1 Recommended Regulatory Action

I recommend an approval action.

In my opinion, the thorough REMS developed by the Agency would substantially mitigate the risk of bronchospasm and related serious outcomes. Under the Agency's Adasuve REMS, loxapine by oral inhalation may only be administered within facilities that have immediate, on-site access to personnel and materials necessary to deliver advanced airway management (including bronchodilator medication via nebulizer, intravenous corticosteroids, intubation, and mechanical ventilation). As part of the REMS, the Agency has developed detailed full prescribing information and instructions for use that that would substantially mitigate the risk of bronchospasm. Labeling includes:

- 1) contraindications regarding patients with pulmonary disease who are at increased risk of developing bronchospasm, 2) a prominent boxed warning and a detailed warning regarding the risk of bronchospasm and measures to mitigate the risk, 3) specific recommendations for thoroughly monitoring patients following treatment, 4) dosing recommendations that limit treatment to one dose within 24 hours, and 5) detailed instructions for use in the full prescribing information and device packaging that include

recommendations for screening and monitoring patients. The REMS requires that enrolled facilities attest to meeting the requirements of the REMS, including providing appropriate training for providers who would administer loxapine. The sponsor is required to develop educational materials for the use of inhaled loxapine. In addition, there are postmarketing requirements for mandatory reporting of bronchospasm and related adverse events.

However, there are potential limitations to the REMS in preventing and fully mitigating the risks of bronchospasm and related serious outcomes. There is a risk that the screening process will not always be ideal. Because of the nature of acute agitation in the intended population, it will not always be possible to obtain a reliable medical history, obtain medical records promptly, or to perform an adequate physical examination to determine if a patient has current respiratory signs/symptoms or is at increased risk of bronchospasm. Furthermore, patients may be potentially at risk for developing bronchospasm after treatment with inhaled loxapine, even if they do not have a history of pulmonary disease; it is possible that they could develop their first episode of bronchospasm following treatment with inhaled loxapine. In addition, it is possible that patients will not always be monitored thoroughly, and they could develop respiratory problems which could go unnoticed. This risk could be increased if the patient becomes sedated. Moreover, in the pulmonary safety studies and efficacy trials, some patients developed significant respiratory adverse reactions (including wheezing) after the first 1 to 2 hours following treatment; some developed respiratory symptoms up to 24 hours following treatment with inhaled loxapine. Thus, it is possible that patients could be discharged and develop complications relatively late. Finally, because bronchospasm can progress rapidly, there is a potential risk that even in a facility with on-site access to full capabilities for advanced airway management, the response to an event might not be immediate, or proper management might not be fully successful.

The pivotal trials in acutely agitated patients with schizophrenia or bipolar disorder clearly demonstrated the efficacy of inhaled loxapine in the treatment of acute agitation associated with schizophrenia or bipolar disorder. Loxapine for oral inhalation may offer unique benefits compared to other available treatments for this indication (i.e., atypical antipsychotics for intramuscular injections). It is critically important to control acute agitation as quickly as possible, because acutely agitated patients are at risk for dangerous behavior toward themselves and others; such behavior can be life-threatening. Treatment with inhaled loxapine results in rapid delivery to the lung and rapid systemic absorption (approaching kinetics with a drug administered intravenously). The onset of efficacy is relatively rapid; significant reductions in the severity of agitation were apparent as early as 10 minutes after dosing, which was the first assessment time point. Although the sponsor did not conduct direct comparisons with injection formulations of antipsychotics, it is widely accepted that there is a significant delay in clinical response with antipsychotic injections used to treat acute agitation. Clinicians often combine the IM antipsychotic with an IM injection of benzodiazepine in a single injection in order to achieve rapid control of agitation. It would be a significant public health benefit to have a treatment option that could provide rapid control of acute agitation. Acute agitation can be severely debilitating and it can lead to violence, physical injury, and death.

Furthermore, this non-invasive treatment could provide distinct safety advantages. The use of intramuscular injections often requires physical restraint and some coercion. During restraint and injection, there is a risk of physical injury to the patient and healthcare providers, including contaminated needle stick injury. With a non-invasive treatment option, there could be a reduced risk of injury. In addition, with this non-invasive treatment option, patients could have a more active role in making decisions about treatment. This in itself has the potential to de-escalate acute agitation and dangerous behavior, and it has the potential to foster the therapeutic alliance between the patient and healthcare provider.

16.2 Recommended Postmarketing Requirements and Commitments

Postmarketing Requirements

Pediatric Assessments:

1. A deferred pharmacokinetic pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. The sponsor must obtain pharmacokinetic data and provide information pertinent to dosing of ADASUVE in the pediatric population.
2. A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. The sponsor must conduct a controlled study of the efficacy and safety of ADASUVE in the relevant pediatric population.
3. The sponsor must conduct a large, non-randomized, open-label, postmarketing observational study to assess the risks of bronchospasm and related respiratory adverse events and serious outcomes (e.g., hospitalization, intubation, mechanical ventilation, or rescue medication for the management of respiratory reactions) associated with ADASUVE treatment. The study must have a large sample size (approximately 10,000 patients exposed to ADASUVE), in order to adequately characterize the frequency, nature, and severity of the risk of bronchospasm (presumably a rare event). The study must assess the use of ADASUVE as used in clinical practice under the requirements of the ADASUVE REMS and per labeling. We must agree prospectively on all aspects of the protocol, including but not limited to: the study design, sample size calculation, patient selection criteria, primary and secondary endpoints, definitions of events, ascertainment of cases, methods for follow-up, required duration of follow-up post-dosing, and the types of patient characteristics and other data to be collected. You must submit all protocol amendments.

Postmarketing Commitments

1. A single-dose GLP developmental juvenile rat tolerability and toxicokinetic study of loxapine by inhalation route that spans the corresponding ages for the pediatric

clinical studies (ages 10 to 17 years). The study must evaluate the potential pharmacodynamic and pharmacokinetic differences among different ages in rats, and the results may apply to potential differences between adults and children.

2. The sponsor must implement, within 6 months of approval, the appropriate controls (routine extraction testing with acceptance criteria) for [REDACTED] ^{(b) (4)} to ensure that levels remain below the levels that have been qualified by the risk assessments in Module 4.

16.3 Special Reporting Requirements for Respiratory Adverse Events

1. The sponsor must submit all initial and follow-up adverse drug experiences pertaining to respiratory events, including but not limited to the following: asthma, COPD, bronchospasm, wheezing, shortness of breath. Additionally, submit reports of respiratory events requiring intervention, such as treatment with a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (invasive and non-invasive), an emergency department visit/prolongation of an existing visit, or hospitalization/prolongation of an existing hospitalization as Postmarketing 15-day “Alert Reports” as defined under 21 CFR 314.80(c).
2. In the periodic reports submitted for the first quarterly reporting period and each subsequent reporting period, the sponsor must include the following:

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

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

/s/

ROBERT L LEVIN
12/10/2012