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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW
Cycle 3 Addendum

Application Type	NDA
Submission Number	22549 SD-47
Submission Code	CR
Letter Date	June 20, 2012
Stamp Date	June 21, 2012
PDUFA Goal Date	December 21, 2012
Reviewer Name	Francis E. Becker, M.D.
Review Completion Date	November 27, 2012
Established Name	Loxapine
Trade Name	Staccato Loxapine for Inhalation (ADASUVE)
Therapeutic Class	Antipsychotic
Applicant	Alexza Pharmaceuticals
Related IND	73248
Priority Designation	Standard

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1. Introduction

ADASUVE (loxapine) inhalation powder (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine represents a new dosage form for loxapine, an antipsychotic with dopamine D_2 blocking activity that has been available in the United States (US) since 1975. *Staccato* Loxapine (5-mg and 10-mg dose levels) has been developed by the sponsor for the treatment of agitation in patients with Schizophrenia or Bipolar Disorder. Since agitation in these psychiatric populations is an acute and intermittent condition, it is expected that patients will be treated with *Staccato* Loxapine on an infrequent basis.

Staccato Loxapine is based on the proprietary *Staccato* delivery system developed by the sponsor. Oral inhalation through the *Staccato* Loxapine for Inhalation product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The resulting rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

This review is a Cycle 3 Clinical Review based on review of the sponsor's Class 2 Complete Response resubmission dated June 21, 2012. Therefore, this review will focus on issues addressed in the Cycle 2 CR letter, the sponsor's response to those issues in Cycle 3, and any updated or revised information provided by the sponsor in this submission which has not been adequately addressed in the previous cycles. For a complete clinical review, the reader is referred to this reviewer's **Cycle 1 Clinical Review** (September 17, 2010), **Cycle 2 Pre-AC Meeting Clinical Review** (November 8, 2011), and **Post-AC Meeting Clinical Review, Cycle 2 Addendum** (April 9, 2012).

2. Regulatory History

The key aspects of the regulatory history of the application are outlined below:

- August 31, 2005: Alexza submitted an IND application (73-248) for *Staccato* Loxapine in the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- December 11, 2009: The sponsor submitted the original NDA (22549) for the treatment of acute agitation associated with schizophrenia or bipolar I disorder.
- October 8, 2010: The Division took a Complete Response action, identifying pulmonary toxicity (bronchospasm) as the primary issue.
- December 17, 2010: The Division and Alexza held an End of Review Meeting to discuss the complete response action and potential means of resolving issues. The Division stated that it would be reasonable to propose a REMS program to mitigate the risk of pulmonary toxicity.

- April 29, 2011: Type C Meeting was held with the sponsor to discuss the possible components of a REMS, including Elements to Assure Safe Use (ETASU).
- August 4, 2011: Alexza submitted a Class 2 Complete Response resubmission. The submission included a REMS with the following components: Elements to Assure Safe Use, revised product labeling, a Medication Guide, a Communication Plan, a Healthcare Facility Certification, an Implementation System, and a timetable for submission of Assessments.
- October 14, 2011: REMS Oversight Committee (ROC) meeting: DRISK and DPP presented the review team's minimum requirements for the ADASUVE REMS program. The committee agreed that ETASU would be required. They also recommended obtaining input from outside stakeholders (from the Drug Safety Board, for example) during the development of the REMS.
- November 16, 2011: Drug Safety Oversight Board (DSB) Meeting – DRISK presented the proposed minimum requirements for the ADASUVE REMS. The board commented on the impact the REMS program might have on their healthcare facilities. The discussion did not result in revisions to the Agency's proposed REMS.
- December 12, 2011: Psychopharmacologic Drugs Advisory Committed (PDAC) Meeting. The committee was supplemented with members of 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 of ADASUVE, and they considered the REMS programs proposed by FDA and the sponsor. The Advisory Committee members voted 9 to 8 (with one abstention) to approve ADASUVE with the FDA-recommended REMS and with limiting administration to one dose within a 24-hour period.
- January 10, 2012: Alexza submitted REMS Amendment #2 to take into consideration and align with the Agency's REMS presented at the PDAC meeting.
- January 19, 2012: The Division decided to extend the review by 3 months, in order to review the REMS (a major amendment to the submission).
- Throughout the review cycle, FDA provided comments to the sponsor about the requirements for the REMS with ETASU. During a teleconference with Alexza on March 1, 2012, the Division clarified that "Immediate, on-site access to advanced airway management capabilities" meant that these capabilities must be available within the healthcare facility in which the product would be administered, as opposed to being available by calling emergency response services.
- April 5, 2012: REMS Oversight Committee (ROC) meeting – DPP and DRISK updated the committee on the DSB and PDAC meetings. The ROC members agreed that ADASUVE could be approved with the finalized REMS. In addition, the ROC recommended that the labeling emphasize the pulmonary risk and discourage inappropriate claims not supported by adequate data (b) (4) .
- April 5, 2012: Alexza submitted a complete proposed protocol for the observational post-marketing study.

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