

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Psychopharmacologic Drugs
Advisory Committee Meeting
December 12, 2011**

Location: Marriott Inn and Conference Center. University of Maryland University College (UMUC) 3501 University Blvd. East, Adelphi, Maryland

Issue: The committee discussed safety and efficacy issues with new drug application (NDA) 022549, ADASUVE (loxapine) inhalation powder, Alexza Pharmaceuticals, Inc., for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Particular issues for discussion were concerns regarding pulmonary safety.

These summary minutes for December 12, 2011 Psychopharmacologic Drugs Advisory Committee Meeting were approved on January 6, 2012

I certify that I attended the December 12, 2011, Psychopharmacologic Drugs Advisory Committee Meeting and that these minutes accurately reflect what transpired.

_____/s/
Philip Bautista, Pharm.D.
Acting Designated Federal Officer, PDAC

_____/s/
Andrew Winokur, M.D., Ph.D.
Acting Chair, PDAC

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting December 12, 2011

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on December 12, 2011. A verbatim transcript will be available in approximately four weeks, sent to the Division of Psychiatry Products and posted on the FDA website at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm277073.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 12, 2011 at the Marriott Inn and Conference Center at University of Maryland University College (UMUC), Adelphi, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Alexza Pharmaceuticals, Inc. The meeting was called to order by Andrew Winokur, M.D., Ph.D. (Acting Chair); the conflict of interest statement was read into the record by Philip Bautista, Pharm.D. (Acting Designated Federal Officer). There were approximately 75 persons in attendance. There were two (2) Open Public Hearing speakers.

Issues: The committee discussed safety and efficacy issues with new drug application (NDA) 022549, ADASUVE (loxapine) inhalation powder, Alexza Pharmaceuticals, Inc., for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Particular issues for discussion were concerns regarding pulmonary safety.

Attendance:

PDAC Members Present (Voting): Matthew Byerly, M.D.; Victor G. De Gruttola, Sc.D.; Christopher J. Kratochvil, M.D.; Joan Luby, M.D.; Elizabeth McCarthy, M.A. (Consumer Representative); Murray B. Stein, M.D., M.P.H.

PDAC Members Not Present (Voting): David A. Brent, M.D.; Helen Egger, M.D.; Michael Y. Hwang, M.D.; Daniel R. Weinberger, M.D.; Tonya Jo Hanson White, M.D.

Temporary Members (Voting): Mark Brantly, M.D.; Dan Budnitz, M.D., M.P.H.; Paula Carvalho, M.D.; Michael Cohen, R.Ph., M.S., Sc.D.; William Greene, Pharm.D.; David Jacoby, M.D.; Jerry Krishnan, M.D., Ph.D.; Margy Lawrence (Patient Representative); Elaine Morrato, M.P.H., D.P.H.; Peter Terry, M.D.; Kenneth Towbin, M.D.; Andrew Winokur, M.D., Ph.D. (Acting Chair)

Acting Industry Representative to the Committee (Non-Voting): William Z. Potter, M.D., Ph.D. (Acting Industry Representative)

FDA Participants (Non-Voting): Ellis Unger, M.D.; Thomas Laughren, M.D.; Mitchell Mathis, M.D.; Theresa Michele, M.D.

Acting Designated Federal Officer (Non-Voting): Philip Bautista, Pharm.D.

Open Public Hearing Speakers: Robert Butz, Ph.D.; Allen Doederlein (President, Depression and Bipolar Support Alliance)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	Andrew Winokur, M.D., Ph.D. Acting Chair, PDAC
Conflict of Interest Statement	Philip Bautista, Pharm.D. Acting Designated Federal Officer, PDAC
FDA Introductory Remarks	Thomas Laughren, M.D. Director Division of Psychiatry Products (DPP) Office of Drug Evaluation I (ODEI) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATION	Alexza Pharmaceuticals, Inc.
Agenda and Overview	Edwin Kamemoto, Ph.D. Executive Director, Regulatory Affairs Alexza Pharmaceuticals
Introduction	James Casella, Ph.D. Senior Vice President Research and Development Alexza Pharmaceuticals
Agitation and Treatment	Scott Zeller, M.D. Chief, Psychiatric Emergency Services Alameda County Medical Center
ADASUVE: A Drug-Device Combination Product	James Casella, Ph.D.
ADASUVE Efficacy Review	James Casella, Ph.D.
ADASUVE Clinical Safety Review	Robert Fishman, M.D., F.C.C.P. Vice President, Clinical Development Alexza Pharmaceuticals
Risk Management Plan for ADASUVE	James Casella, Ph.D.
Closing Remarks	Leslie Zun, M.D., M.B.A. Chair, Department of Emergency Medicine Mount Sinai Hospital Chicago
Clarifying Questions	

BREAK

FDA PRESENTATION

Clinical Overview

Francis E. Becker, M.D., F.A.C.P.
Medical Officer
DPP, ODEI, OND, CDER, FDA

Pulmonary Safety of ADASUVE

Theresa Michele, M.D.
Clinical Team Leader
Division of Pulmonary, Allergy and
Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODEII)
OND, CDER, FDA

Risk Evaluation and Mitigation Strategy (REMS)
for ADASUVE

Kimberly Lehrfeld, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk
Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing Session

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

- 1) Adasuve is intended to be a rapidly acting antipsychotic for use in treating agitation. There are, however, no direct comparisons of Adasuve with other products approved for the treatment of agitation in patients with schizophrenia or bipolar mania.
 - a. Is it possible to make valid comparisons of the onset of effect for Adasuve and other drugs in the class in the absence of head-to-head studies? **(DISCUSSION)**
 - b. If yes, how does time of onset of this product compare with that of other products approved for this indication? Is this difference a substantial advantage? **(DISCUSSION)**

Committee Discussion of #1a and #1b: *The consensus view of the committee was that it is not possible to make valid comparisons of the onset of effect between Adasuve and the other drugs in the class already approved for this indication without head-to-head studies. Furthermore, the committee felt that it would not be possible to make a judgment on this question based solely on the pharmacokinetic profile of Adasuve. However, the committee agreed that the drug product has the advantage of being less invasive than parenteral treatments and would likely be a more acceptable option to patients. Please see the transcript for details of the committee discussion.*

- c. Would comparative studies with currently approved intramuscular products be needed to demonstrate an advantage(s) for this product? **(DISCUSSION)**

Committee Discussion: *Although some committee members felt that comparative studies with currently approved intramuscular products may be useful, there was no consensus on this question. Please see the transcript for details of the committee discussion.*

- 2) Adasuve clearly can cause bronchospasm, a particular concern for patients with asthma. There is uncertainty as to whether agitated patients can be properly assessed for an asthma history. Do you think the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) would ensure that the benefits of Adasuve outweigh its risks? **(DISCUSSION)**
 - a. If yes, could the REMS be less burdensome and still accomplish the level of safety necessary to ensure safe use of this product? **(DISCUSSION)**
 - b. If no, would strengthening the REMS ensure that the benefits of Adasuve outweigh its risks? How should the REMS be strengthened? **(DISCUSSION)**
 - c. Would additional steps, beyond strengthening REMS, be needed? **(DISCUSSION)**

Committee Discussion: *There appeared to be a consensus on the committee that the sponsor's proposed REMS would not ensure that the benefits of Adasuve outweigh its risks. The committee also agreed that additional steps to strengthen the REMS, including those proposed by the FDA, would be necessary to ensure that the product could be used safely. The committee expressed concern that, in certain settings, such as an emergency room, proper screening of patients may not always be possible. The committee agreed that there was a possibility that patients with underlying airway hyperresponsiveness may be missed during the screening process and inadvertently given Adasuve. Some of the pulmonologists on the committee were specifically concerned by the lack of data to demonstrate what would occur if asthmatic patients were exposed to additional doses of Adasuve given 2 hours apart as permitted by the proposed product label. Please see the transcript for details of the committee discussion.*

- 3) Does the committee have any recommendations regarding the proposed post-marketing observational study? Should an observational study be considered a preapproval requirement, or would it be sufficient to conduct such a study post-approval? **(DISCUSSION)**

Committee Discussion: *Some on the committee agreed that more data was necessary, specifically data from the use of Adasuve in emergency room settings. There was some*

discussion of the details of such a study, and a general consensus that it need not be a comparative study. Rather, the committee felt that it was more important to have a reasonably sized cohort of patients screened and treated with Adasuve in an emergency room setting. However, no consensus was reached on whether an observational study should be considered a pre-approval requirement or whether it would be sufficient to conduct such a study post-approval. Given that the sponsor's proposed dose (10 mg every 2 hours, up to 3 doses in 24 hours) was not studied in patients with asthma or COPD, some of the pulmonologists on the committee raised concern that approving this drug product without additional data would pose an unknown risk to this patient population if they were to accidentally receive it. Some of the pulmonologists suggested that their concerns would be lessened if the dosing could be limited to only one dose in 24 hours, until further data is collected. Please see the transcript for details of the committee discussion.

- 4) Does the committee conclude that Adasuve (loxapine) inhalation powder has been shown to be effective as a treatment for agitation in patients with schizophrenia or bipolar mania? **(VOTE: Yes/No/Abstain)**

Vote: Yes= 17 No = 1 Abstain = 0

Committee Discussion: *An overwhelming majority of the committee agreed that Adasuve (loxapine) inhalation powder had been shown to be effective as a treatment for agitation in patients with schizophrenia or bipolar mania. Please see the transcript for details of the committee discussion.*

- 5) Does the committee conclude that Adasuve (loxapine) inhalation powder has been shown to be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania:

- a. When used in conjunction with the REMS proposed by the sponsor? **(VOTE: Yes/No/Abstain)**

Vote: Yes= 1 No = 17 Abstain = 0

- b. When used in conjunction with the REMS proposed by FDA? **(VOTE: Yes/No/Abstain)**

Vote: Yes= 5 No = 12 Abstain = 1

Committee Discussion: *At the current sponsor proposed dose (10 mg every 2 hours, up to 3 doses in 24 hours), the majority of the committee agreed that Adasuve (loxapine) inhalation powder had not been shown to be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with either the sponsor proposed or the FDA proposed REMS. There were concerns that there were not enough data to support the safe use of two doses within 2 hours, especially when the effectiveness of screening patients in an emergency room setting was not well-established. Please see the transcript for details of the committee discussion.*

- 6) *Based on the discussions that transpired, the following question was added during the meeting:* If the product was limited to a single dose in 24 hours, does the committee conclude that Adasuve (loxapine) inhalation powder would be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with the REMS proposed by FDA? **(VOTE: Yes/No/Abstain)**

Vote: **Yes= 11** **No = 5** **Abstain = 2**

Committee Discussion: *The majority of the committee agreed that a single dose of Adasuve (loxapine) inhalation powder in 24 hours would be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania when used in conjunction with the REMS proposed by FDA. However, some of the pulmonologists on the committee still disagreed as they felt that there was not enough information on the safety of even one dose in emergency room settings. Please see the transcript for details of the committee discussion.*

- 7) Does the committee conclude that Adasuve (loxapine) inhalation powder should be approved for use as a treatment for agitation in patients with schizophrenia or bipolar mania? **(VOTE: Yes/No/Abstain)**

Based on the discussions that transpired, question #7 was skipped.

- 8) Is a REMS necessary to ensure that the benefits of Adasuve outweigh the risks? **(VOTE: Yes/No/Abstain)**

Based on the discussions that transpired, question #8 was skipped.

- 9) *Based on the discussions that transpired, the following question was added during the meeting:* Does the committee conclude that Adasuve (loxapine) inhalation powder should be approved for use as a single dose in 24 hours when used with the FDA proposed REMS as a treatment for agitation in patients with schizophrenia or bipolar mania? **(VOTE: Yes/No/Abstain)**

Vote: **Yes= 9** **No = 8** **Abstain = 1**

Committee Discussion: *A slight majority of the committee was in favor of approving Adasuve as a single dose in 24 hours when used with a REMS as proposed by FDA, given the data now available. The primary disagreement was in regard to the safety of even a single dose despite having the FDA proposed REMS in place. The committee members who voted “No” indicated that an observational study involving a cohort of patients treated with this product in an emergency room setting would be needed prior to approval. Other committee members felt that such a study was not needed as a pre-approval requirement. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:45 p.m.