

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022549Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 022549
Product Name: Adasuve (loxapine) inhalation powder

PMR/PMC Description: 1891-1
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.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	5/1/2013
Study/Trial Completion:	7/18/2013
Final Report Submission:	1/18/2014
Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

We are deferring submission of the pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to obtain pharmacokinetic data and provide information pertinent to dosing of ADASUVE in the relevant population (pediatric population).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☒ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	022549
Product Name:	Adasuve (loxapine) inhalation powder
PMR/PMC Description:	1891-2 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.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 10/1/2013
	Study/Trial Completion: 9/30/2014
	Final Report Submission: 3/30/2014
	Other: NA

- During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
 - ☐ Unmet need
 - ☐ Life-threatening condition
 - ☐ Long-term data needed
 - ☒ Only feasible to conduct post-approval
 - ☐ Prior clinical experience indicates safety
 - ☐ Small subpopulation affected
 - ☐ Theoretical concern
 - ☐ Other
- Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

We are deferring submission of the pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study of the efficacy and safety of ADASUVE in the relevant pediatric population.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	022549
Product Name:	Adasuve (loxapine) inhalation powder
PMR/PMC Description:	1891-3 You are required to 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 for respiratory adverse reactions, intubation, and mechanical ventilation) associated with ADASUVE treatment.
PMR/PMC Schedule Milestones:	Final Protocol Submission: 6/1/2013
	Study/Trial Completion: 6/1/2015
	Final Report Submission: 12/1/2015
	Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- ☒ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	022549
Product Name:	Adasuve (loxapine) inhalation powder
PMR/PMC Description:	1891-4 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).
PMR/PMC Schedule Milestones:	Final Protocol Submission: NA
	Study/Trial Completion: NA
	Final Report Submission: 5/31/2013
	Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The study will evaluate the potential pharmacodynamic and pharmacokinetic differences among different ages in rats, and the results may apply to potential differences between adults and children.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A single dose inhalation tolerability and toxicokinetic study in the rat, (b) (4)
(b) (4) that span the corresponding ages proposed for the pediatric pharmacokinetic and efficacy trials (10 – 17 years).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☒ Nonclinical study, not safety-related (specify)
A single-dose GLP developmental juvenile rat tolerability and toxicokinetic study.
 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #	022549
Product Name:	Adasuve (loxapine) inhalation powder
PMR/PMC Description:	1891-5 Implement, within 6 months of approval, the appropriate controls (routine extraction testing with acceptance criteria) for (b) (4) to ensure that levels remain below the levels that have been qualified by the risk assessments in Module 4.
PMR/PMC Schedule Milestones:	Final Protocol Submission: NA Study/Trial Completion: NA Final Report Submission: 4/30/2013 Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial

- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☒ Other

The results of the extractables studies on the process validation drug product batches will be used to guide the applicant to developing routine controls for the named volatile compounds that can potentially be emitted during patient use.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022549	NDA Supplement #: NA	Efficacy Supplement Type: NA
Proprietary Name: Adasuve Established/Proper Name: loxapine inhalation powder Dosage Form: inhalation powder Strengths: 10mg		
Applicant: Alexza Pharmaceuticals		
Date of Receipt: 6/21/2012 (Complete Response) (Original submission - 12/11/2009; 1 st cycle CR 8-4-2011; 2 nd cycle CR 5-2-2012)		
PDUFA Goal Date: 12/21/2012		Action Goal Date (if different): Early/Mid November
Proposed Indication(s): Acute Treatment of Agitation Associated with Schizophrenia or Bipolar		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Loxitane (NDA 017525)	NonClinical Safety Information
Loxitane IM (NDA 018039)	NonClinical Safety Information

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s).

Alexza conducted a 14 day inhalation study in rat (Study # N106043) and a 28 day inhalation study in dog (Study # 78670) demonstrating that systemic exposure was achieved following this route of administration, and that the overall toxicity profile was not appreciably different than that observed following oral administration. Alexza conducted an in vitro metabolism study demonstrating that no novel metabolites were generated in lung microsomes as compared to liver microsomes (Study # AZ004-DM-003).

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Loxitane	NDA 017525	Y
Loxitane IM	NDA 018039	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing: **Loxitane Capsules, Loxitane IM**

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new dosage form, from capsule or injectable, to powder for inhalation. This application also provides for a new indication, acute treatment of agitation associated with bipolar or schizophrenia.

[The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.]

[The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.]

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☒

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are

listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
--

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- ☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

KIMBERLY S UPDEGRAFF
12/19/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	ADASUVE (loxapine) inhalation powder, for oral inhalation use
Applicant	Alexza Pharmaceuticals, Incorporated
Application/Supplement Number	NDA 022549
Type of Application	Resubmission/Class 2
Indication(s)	Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.
Established Pharmacologic Class ¹	Typical antipsychotic
Office/Division	ODEI/DPP
Division Project Manager	Kim Updegraff
Date FDA Received Application	June 21, 2012
Goal Date	December 21, 2012
Date PI Received by SEALD	December 12, 2012
SEALD Review Date	December 13, 2012
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

NO

1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Correct margin at the top of HL to be 1/2 inch. Currently the margin is greater than 1/2 inch.*

YES

2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DPP to grant waiver of 1/2 page HL limit in approval letter.*

YES

3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES

4. White space must be present before each major heading in HL.

Comment:

YES

5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

Selected Requirements of Prescribing Information

- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Selected Requirements of Prescribing Information

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

YES

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

DEBRA C BEITZELL
12/13/2012

LAURIE B BURKE
12/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Study Protocol

Date:	November 27, 2012
Reviewer(s):	Cary Parker, M.P.H., Epidemiologist Division of Epidemiology I
Team Leader	Simone P. Pinheiro, Sc.D., M.Sc., Associate Director, Team Leader Division of Epidemiology I
Division Director	Solomon Iyasu, M.D., M.P.H., Director Division of Epidemiology I
Subject	Review of observational study protocol entitled, “A Post-Marketing Observational Study to Evaluate the Safety of ADASUVE (<i>Staccato</i> loxapine for inhalation) in Agitated Patients with Schizophrenia or Bipolar Disorder” – Version 0.3, Dated 30-MAR-2012
Drug Name(s):	Adasuve (<i>Staccato</i> loxapine)
Application Type/Number:	NDA 022549
Applicant/sponsor:	Alexza Pharmaceuticals, Inc.
OSE RCM #:	2012-1770 (related to OSE RCM #2011-3482)

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EXECUTIVE SUMMARY

Alexza Pharmaceuticals, Inc. submitted NDA 022549 to support the approval of Adasuve (*Staccato* loxapine), an oral inhalation prescription drug product for the treatment of acute agitation associated with schizophrenia or bipolar disorder in adults. If approved, the sponsor will be required to conduct a post-marketing observational study to assess the primary safety concern of pulmonary toxicity (e.g. bronchospasm) of Adasuve treatment in real-world clinical settings. In this review, the Division of Epidemiology in the Office of Surveillance and Epidemiology (DEPI/OSE) assessed the study protocol, identified several issues of concern, and provided a list of recommendations to be addressed by the sponsor. Specifically, the sponsor should address (b) (4)

(b) (4) In addition, DEPI recommends that the sponsor collect (b) (4)

, DEPI recommends that the sponsor collects (b) (4)

1 INTRODUCTION

Alexza Pharmaceuticals, Inc. submitted NDA 022549 to support the approval of Adasuve (*Staccato* loxapine) to the Division of Psychiatry Products in the Office of New Drugs (DPP/OND). If approved, the sponsor will be required to conduct a post-marketing observational study to assess safety concerns. DPP requested that the Division of Epidemiology in the Office of Surveillance and Epidemiology (DEPI/OSE) provide input regarding the proposed post-marketing requirement (PMR) observational study protocol, which is the subject of this review.

1.1 BACKGROUND

On December 11, 2009, Alexza Pharmaceuticals, Inc. (Alexza) submitted NDA 022549 to support the approval of Adasuve (*Staccato* loxapine), an oral inhalation prescription drug product for the treatment of acute agitation associated with schizophrenia or bipolar disorder in adults. This product introduces a new medical delivery system for loxapine. *Staccato* loxapine is a single use, hand held device product that provides rapid systemic delivery of loxapine through absorption in the lung. Pulmonary safety data for Adasuve (*Staccato* loxapine) has been reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)¹. According to DPARP's review¹ of the pulmonary safety trials, the use of Adasuve was demonstrated to cause pulmonary toxicity (e.g., bronchospasm) not only in healthy volunteers, but also, and to a greater extent, in patients with history of lung disease (e.g. asthma, chronic obstructive pulmonary disease).

¹ Michele TM. "Pulmonary safety evaluation of Adasuve (loxapine) inhalation powder for New Drug Application (NDA) 22-549 at a dose of 5 mg or 10 mg every 2 hours as needed to a maximum dose of 30 mg per day for the treatment of agitation associated with schizophrenia or bipolar disorder in adults." Submitted 03/06/2011. DARRTS Reference ID 3108649.

Due to the primary safety concern of pulmonary toxicity, the Division of Psychiatry Products in the Office of New Drugs (DPP/OND) issued a Complete Response (CR) Action Letter on October 8, 2010, and subsequently held an End of Review Meeting on December 17, 2010 and a Type C Meeting on April 29, 2011 with the sponsor to discuss how the issues highlighted in the CR Action Letter could be addressed. On August 4, 2011, the sponsor provided a resubmission of NDA 022549, including a proposed risk management plan to address the primary safety concern of pulmonary toxicity. The proposed risk management plan consisted of three parts: 1) Updated draft labeling; 2) A proposed Risk Evaluation & Mitigation Strategy (REMS) including a Medication Guide, a multi-component communication and education plan, and an Element to Assure Safe Use (ETASU); 3) A brief observational study protocol synopsis².

On November 3, 2011, the Division of Epidemiology in the Office of Surveillance and Epidemiology (DEPI/OSE) submitted a review³ of the observational study protocol synopsis. On December 12, 2011, a Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting was convened for Adasuve. The committee voted to recommend that Adasuve be approved for use as a single dose in 24 hours when used with FDA's proposed more restrictive version of the REMS. The PDAC vote on approval of Adasuve was 9/8/1 (yes/no/abstain).

The FDA proposed a REMS and labeling to minimize the risk of bronchospasm related to use of Adasuve. Elements of this proposed REMS include a) limit dispensing to only specially certified health care settings that have immediate access on-site to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation; b) screen patients and avoid use of Adasuve in patients at highest risk of bronchospasm; c) ensure appropriate personnel and equipment are available to treat bronchospasm; d) monitor respiratory and heart rate and perform chest auscultation on patients post-dose every 15 minutes for first hour and every 30 minutes thereafter; e) implement a detailed communication plan targeting likely prescribers including psychiatrists and Emergency Department physicians.

On May 2, 2012, another CR Action Letter was issued due to deficiencies in manufacturer's facility inspections. FDA also requested updated documents including labeling, REMS, and post-marketing study protocol details. On April 6, 2012, the sponsor submitted a more detailed post-marketing observational study protocol,⁴ which is the subject of this review.

² ALEXZA Pharmaceuticals, Inc., ADASUVE (staccato loxapine for inhalation), Protocol No. AMDC 004-401 – "A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of *Staccato* Loxapine in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings – Protocol Synopsis." Submitted 08/04/2011.

³ Parker C. Review of draft observational study protocol synopsis entitled, "A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of Staccato Loxapine in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings." Submitted 11/03/2011. OSE RCM # 2011-3482. DARRTS Reference ID 3039272.

⁴ ALEXZA Pharmaceuticals, Inc., ADASUVE (staccato loxapine for inhalation), Protocol No. AMDC 004-401 – "A Post-Marketing Observational Study to Evaluate the Safety of ADASUVE (staccato loxapine for inhalation) in

1.2 REGULATORY HISTORY

- **December 11, 2009:** NDA submitted to FDA
- **October 8, 2010:** CR Action taken, identifying pulmonary toxicity as the primary safety concern
- **December 17, 2010:** End of Review Meeting with the sponsor to discuss how the CR issues could be resolved
- **April 29, 2011:** Type C Meeting
- **August 4, 2011:** Resubmission of NDA with proposed risk management plan to address the primary safety concern of pulmonary toxicity
- **November 3, 2011:** In preparation for the PDAC Meeting, DEPI submitted review of observational study protocol synopsis
- **December 12, 2011:** PDAC Meeting – results: committee voted 9/8/1 (yes/no/abstain), in favor of approval
- **May 2, 2012:** Another CR Action taken due to deficiencies in facility inspections by Center for Devices and Radiological Health (CDRH) and FDA requests for updated documents including labeling, REMS requirements, and post-marketing observational study protocol details

2 REVIEW METHODS AND MATERIALS

The current review assessed this version of the sponsor's study protocol:

- Alexza Pharmaceuticals, Inc., Adasuve (*Staccato* loxapine for inhalation), Protocol No. AMDC 004-401 – “A Post-Marketing Observational Study to Evaluate the Safety of Adasuve (*Staccato* loxapine for inhalation) in Agitated Patients with Schizophrenia or Bipolar Disorder – Observational Study Protocol – Version 0.3, Draft Date 30-MAR-2012.” Submitted 04/06/2012.

3 REVIEW RESULTS

(b) (4)

Agitated Patients with Schizophrenia or Bipolar Disorder – Observational Study Protocol – Version 0.3, Draft Date 30-MAR-2012.” Submitted 04/06/2012.

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/s/

CARY C PARKER
11/27/2012

SIMONE P PINHEIRO
11/27/2012

SOLOMON IYASU
11/27/2012

**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**

Label, Labeling and Packaging Memorandum

Date: October 11, 2012

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Adasuve (Loxapine) Inhalation Powder
10 mg

Application Type/Number: NDA 022549

Applicant: Alexza Pharmaceuticals, Inc.

OSE RCM #: 2012-1688

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

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1 INTRODUCTION

This review evaluates the device label, pouch labeling, carton labeling and instructions for use received on June 21, 2012 for Adasuve, NDA 022549, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

DMEPA previously completed reviews of the Adasuve labels and labeling in OSE Review 2010-87-1, dated March 12, 2012, and OSE Review 2012-629, dated April 9, 2012, which were followed by label and labeling negotiations with the Applicant. A Complete Response (CR) action was taken on May 2, 2012. On June 21, 2012, the Applicant responded to the CR and, in that submission, included the revised labels and labeling that had been negotiated. (b) (4)

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the device label, pouch labeling, carton labeling, and instructions for use received on June 21, 2012 (see Appendix A). We compared those labels and labeling against the recommendations contained in OSE Reviews 2010-87-1 and 2012-629 and our follow up labeling negotiations.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the labels and labeling received on June 21, 2012 determined that the Applicant has implemented all of our previous recommendations and agreed upon changes to the labels and labeling. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, Project Manager, at 301-796-2445.

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/s/

LORETTA HOLMES
10/11/2012

IRENE Z CHAN
10/12/2012

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 17, 2010

TO: Kimberly Updegraff, Regulatory Project Manager
Robert Levin, MD, Medical Officer Team Leader
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-549

APPLICANT: Alexza Pharmaceuticals, Inc.

DRUG: loxapine (Staccato®) for inhalation

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: (1) adult schizophrenia patients with agitation,
(2) adult bipolar I disorder patients with acute agitation

CONSULTATION REQUEST DATE: February 10, 2010

DIVISION ACTION GOAL DATE: August 8, 2010

PDUFA DATE: October 11, 2010

I. BACKGROUND:

Agitation is a disruptive and morbid complication of schizophrenia, mania and dementia. Acute agitation is treated pharmacologically with antipsychotics and/or benzodiazepines, available in formulations such as oral tablets or liquids, orally disintegrating tablets, and intramuscular injections. The onset of action after oral or intramuscular administration of commonly used therapeutics is typically 30-60 min due to slow absorption into the systemic circulation. A slow onset of drug action may increase the need for physical restraint or seclusion in an agitated patient. Inhalational drug delivery with anti-agitation medications such as loxapine, a D2 receptor antagonist, would be an alternative agent.

The sponsor submitted this application in support of the use of loxapine in the treatment of acute agitation associated with schizophrenia and acute bipolar I disorder. Two adequate and well-controlled studies were submitted in support of the application as summarized below.

Protocol AMDC-004-301 (schizophrenia protocol)

Study 004-301 was a Phase 3, pivotal, in-patient, multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and efficacy study. Eligible patients were randomized (1:1:1) to loxapine 5 mg or 10 mg, or placebo, and Dose 1 of study medication was then administered. A maximum of 3 doses of study medication were allowed over the 24-hour evaluation period, with Doses 2 and 3 administered only if needed. The purposes of the study were (a) to confirm the safety and efficacy of loxapine at 5- and 10-mg dose levels in the treatment of acute agitation in schizophrenic patients, and (b) to confirm the tolerability of up to 3 doses administered in a 24-hour period.

The study was conducted at 24 sites in the United States. The study period was from February 22, 2008 (first patient randomized) until June 27, 2008. The primary efficacy endpoint was the absolute change in PEC score from baseline to two hours following Dose 1 of loxapine, compared with placebo. Patients at baseline required a Positive and Negative Symptom Scale Excited Component (PEC) total score of greater or equal to 14, with a score of greater or equal to 4 on at least 1 of the 5 items of the PEC scale.

Protocol AMDC-004-302 (mania protocol)

Study 004-302 was a Phase 3, pivotal, in-patient, multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and efficacy study. Eligible patients were randomized (1:1:1) to loxapine 5 mg or 10 mg, or placebo, and Dose 1 of study medication was then administered. A maximum of 3 doses of study medication were allowed over the 24-hour evaluation period, with Doses 2 and 3 administered only if needed. The purposes of the study were (a) to confirm the safety and efficacy of loxapine at 5 mg and 10 mg dose levels in the treatment of acute agitation in patients with a diagnosis of bipolar I disorder (manic or mixed episodes) as defined by DSM-IV criteria, and (b) to confirm the tolerability of up to 3 doses administered in a 24-hour period.

The study was conducted at 17 sites in the United States. The study period was from July 24, 2008 (first patient randomized) until November 2, 2008. The primary efficacy endpoint was the absolute change in PEC score from baseline to two hours following Dose 1 of loxapine, compared with placebo. Patients at baseline required a Positive and Negative Symptom Scale Excited Component (PEC) total score of greater or equal to 14, with a score of greater or equal to 4 on at least 1 of the 5 items of the PEC scale.

Two domestic clinical sites were selected for inspection because these clinical sites enrolled a large numbers of study subjects. While this is not a new molecular entity, however, treatment with the inhalational form of the drug product for the indications is novel. Both clinical investigators participated in well-controlled studies of efficacy and safety studies: AMDC-004-301 and AMDC-004-302, respectively.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site	Insp. Date	EIR Received Date	Final Classification
Richard L. Jaffe, MD	Philadelphia, PA	Study 004-301 Site #10 Study 004-302 Site #08	April 22-27, 2010	May 6, 2010	No Action Indicated (NAI)
Adam F. Lowy, M.D.	Washington, DC	Study 004-301 Site #17 Study 004-302 Site #12	May 5-17, 2010	June 9, 2010	Voluntary Action Indicated (VAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Richard Louis Jaffe, MD

Belmont Center for Comprehensive Treatment
4200 Monument Road
Philadelphia, PA 19131

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from April 22 - 27, 2010, and both “pivotal” studies were inspected.

For PROTOCOL AMDC-004-301 (schizophrenia protocol), a total of 19 subjects were screened, 15 were randomized and completed the study. There were no deaths and SAEs reported. An audit of 15 enrolled study subjects was conducted.

For PROTOCOL AMDC-004-302 (mania protocol), a total of 26 subjects were screened, 18 were randomized and completed the study. There were no deaths and SAEs reported. An audit of 18 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, from both “pivotal” studies, appear acceptable for this specific indication.

2. Adam F. Lowy, M.D.

Comprehensive Neuroscience, Inc.
Psychiatric Institute of Washington
4228 Wisconsin Ave, NW
Washington, DC 20016

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from May 5- 17, 2010. Both “pivotal” studies were inspected for this application at this site.

For PROTOCOL AMDC-004-301 (schizophrenia protocol), a total of 5 subjects were screened, 5 were randomized, and 5 subjects completed the study. There was no under-reporting of adverse events. An audit of 100% of enrolled study subjects was conducted.

For PROTOCOL AMDC-004-302 (mania protocol), a total of 14 subjects were screened, 13 were randomized, and 13 subjects completed the study. There was no under-reporting of adverse events. An audit of 100% of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. At the end of the inspection, a one-observation Form FDA 483 was issued that was relevant to Protocol AMDC 004-301. Specifically, (a) for Subject #17-109, consent form was signed by subject on March 26, 2008, but subject screening printout of the ECG was dated March 25, 2008, and (b) for Subject #17-110, consent form was signed on March 28, 2008, but subject screening printout of the ECG was dated March 27, 2008. While these are considered regulatory deficiencies with respect to accurate records, the findings are considered minor and isolated in nature and of no substantive impact on the conduct of this clinical trial protocol. Otherwise, inspection revealed compliance with efficacy data, adverse event reporting, test article accountability, and adherence to protocol specified procedures for randomization.

Study AMDC-004-302 was conducted appropriately, and no significant issues were identified.

d. Data acceptability/reliability for consideration in the NDA review decision.

Although regulatory deficiencies were noted with respect to Protocol AMDC 004-301, the findings are considered minor and isolated in occurrence, and it is unlikely that these would impact data reliability. The data, in support of clinical efficacy and safety from this clinical site for both “pivotal” studies, appear acceptable for this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections two U.S. clinical investigator sites were inspected in support of this application, for Protocols AMDC-004-301 (schizophrenia protocol) and AMDC-004-302 (mania protocol), respectively. No significant regulatory violations that would importantly impact data integrity were noted. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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/s/

ANTHONY J ORENCIA
08/19/2010

TEJASHRI S PUROHIT-SHETH
08/20/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 30 JUL 2012

FROM: David J. Claffey, PhD

SUBJECT: Evaluation of Impact of failures in the process
validation (b) (4) on the 10 mg strength product

(b) (4)

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/s/

DAVID J CLAFFEY
08/06/2012

RAMESH K SOOD
08/06/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: March 23, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Kim Updegraff, Regulatory Project Manager, CDER/OND/ODEI/DPP

SUBJECT: **NDA 022549**
Applicant: Alexza Pharmaceuticals
Device Constituent: Loxapine Inhaler
Intended Treatment: Schizophrenia and bipolar


QuynhNhu Nguyen, Combination Products Human Factors Specialist

3/23/2012
Date


Ron Kaye, Human Factors and Device Use-Safety Team Leader

3/23/2012
Date

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CDRH Human Factors Review

Overview

The Division of Psychiatry Products requested a Human Factors consultative review of the NDA 22549 submitted by Alexza Pharmaceuticals. On 12/3/11, the Division sent an Information Request letter containing comments regarding the Human Factors study as provided by CDRH and DMEPA. The sponsor repeated the study as advised and has submitted the results for review. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA.

Review Materials

\\CDSESUB1\EVSPROD\NDA022549\0037

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 22549
Applicant: Alexza Pharmaceuticals
Drug Constituent: Adasuve (loxpine)
Dosage form: powder/thin film
Route of administration: oral inhalation
Device Constituent: Inhaler
Intended treatment: Schizophrenia and Bipolar

CDRH Human Factors Involvement History

- 1-NOV-2012: CDRH HF was requested to provide a review on the Human Factors information contained in the NDA
- 3-DEC-2012: CDER issued in Information Request letter containing Human Factors deficiencies
- 14-MAR-2012: CDRH HF was requested to provide a review on Alexza's response to Human Factors deficiencies

Review of Human Factors Related Information

In a cover letter dated 06-MAR-2012, Alexza Pharmaceuticals indicated that in this response, they have implemented changes to the product design, device labeling, pouch labeling and instructions for use. In addition, they submitted results of additional human factors testing to demonstrate how the revisions support safe and effective use.

Summary of Prior Human Factors Validation Study

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, Alexza has undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. They changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- [REDACTED] (b) (4)
- [REDACTED]

Furthermore, many of the HCPs provided comments regarding how the design could be further improved. For example:

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

While the Agency recognizes that Alexza has taken helpful measures in its effort to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that Alexza to take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Improvements should be demonstrated through focused HF/usability validation.

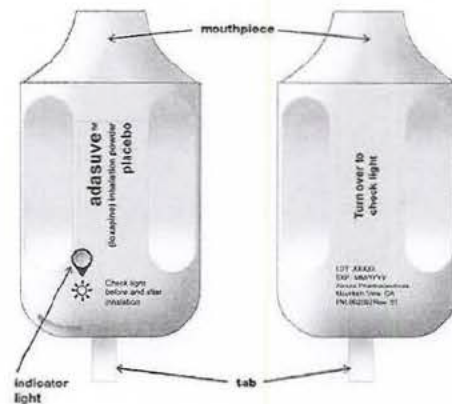
Summary of Human Factors Retesting Due to Changes to Design, IFU, and Labeling

The following tables provide a summary of the changes made to the product design, IFU, and labeling.

(b) (4)



The following image depicts the current location of the green light, and a label that indicates its significance in the use of the product.



These changes were validated in additional Human Factors studies (referred Study 2 and Study 3 in the submission) that were conducted with Healthcare Providers (HCP).

Study 2 Results

Based on changes to the tear-notch location and revisions to the IFU, Alexza conducted Study 2 to validate the changes. Out of the 6 directed tasks, 3 were completed successfully by each HCP participant. In the other 3 directed tasks, all of which were intentional non-normal "challenge" scenarios, there were 4 cases where the task failure was due to a use error, and these occurred during the "challenge" scenarios. In one instance, the HCP did not check the status of the LED prior to having the standard patient inhale; and in the other instances, the HCP did not check the status of the LED after the standard patient inhaled and therefore did not see that the LED was still on.

In addition to the use errors leading to the designation of a task as a failure, there were some additional use errors observed. 10 of the 15 representative HCPs committed a total of 21 use errors out of the 90 tasks. (b) (4)

Study 2 results show similar task failures and use errors to previous Human Factors validation study, which indicated that device design, IFU, and labeling could be further optimized. As a result, Alexza implemented additional changes and validated those changes in Study 3.

Study 3

(b) (4)

Out of the 6 directed tasks, 5 were completed successfully by each HCP participant.

(b) (4)

Six of the 15 representative HCPs committed a total of 9 use errors out of the 90 tasks. The most prevalent use errors previously were related to checking the status of the LED indicator either after removing the pull tab or after the standard patient inhaled. For these cases, the HCP provided complete inhalation instructions for the first inhalation through the device. Upon noticing that the device did not actuate, these HCPs provided abbreviated instructions for the re-inhalation maneuver, often focusing on what they perceived as the cause of the non-actuation, i.e. the standard patient not inhaling adequately.

CDRH Human Factors Review Final Recommendations

The sequential Human Factors studies showed that the use errors have decreased significantly which were attributed to the device and IFU changes that Alexza implemented. Many of the use errors that were originally observed have been eliminated, and the only errors remaining (forgetting to check the status of the green LED turning on, providing incomplete inhalation instructions) are effectively minimized. Feedback from representative users has improved. The root-cause analyses of the residual use errors show that additional changes to the device or IFU would likely not affect the usability or use-safety of the product.

The reviewer believes that the remaining risks associated with the use of the device are acceptable, and further mitigations are not necessary. The sequential Human Factors study demonstrated that use-related risks have been effectively minimized through design and IFU/labeling changes. The study results were found acceptable.

Appendix 1 – Previous CDRH Human Factors Reviews and Evaluations

DATE: November 1, 2011
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
TO: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
SUBJECT: Nayan Patel, Biomedical Engineer, CDRH/ODE/DAGID/ARDB
CTS Consult: NDA 022549 Staccato Loxapine – Inhalation (Psychiatric Patients)
CON118063- Human Factors/Usability Review

Per your request, I have reviewed the Human Factors information pertaining to the proposed product. Please request the sponsor to provide additional information for the concerns outlined in the recommendation section, page 13.

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Evaluation of Human Factors Information

Overview

The Division of Psychiatry Products (CDER) has requested a consult from CDRH regarding the review of an NDA submission, # 022,549, Staccato Loxapine manufactured by Alexza Pharmaceuticals, Inc. This is a re-submission based on the Agency's Complete Response letter issued 10/6/2011. The CR letter consisted of a request for a human factors validation study along with two other requests for device performance testing.

For this resubmission, Nayan Patel is the device lead reviewer and he has consulted this reviewer to evaluate the Human Factors information provided in the submission. This review will focus on the sponsor's response to the Human Factors request.

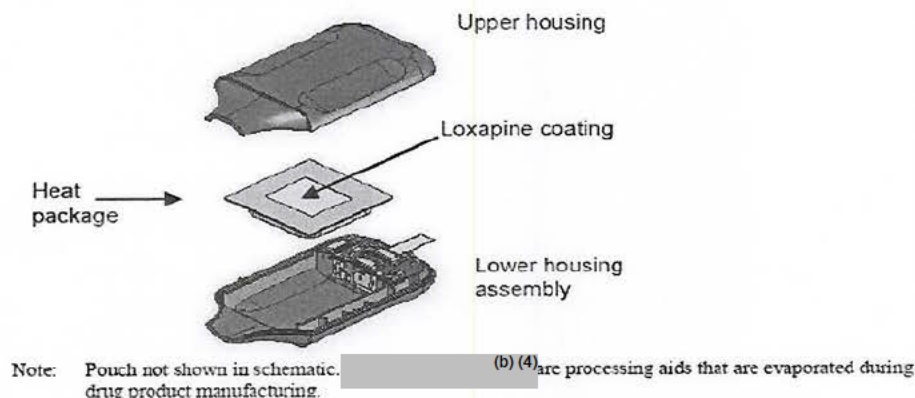
Device Description

Staccato® Loxapine for Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg.

Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza. Oral inhalation through the 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 rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

Staccato Loxapine (5 mg and 10 mg) has been developed 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.

Figure 1. Schematic of *Staccato* Loxapine



Intended Use

The proposed combination product is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder.

Summary of Human Factors Information

The sponsor submitted Human Factors test protocol and report in the resubmission of the NDA. The following paragraphs outline the CDRH HF request and evaluation of the HF information provided in the resubmission.

CDRH's Human Factors Request

1. Based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, a prominent visible flash, and elevated inspired air temperature. These phenomena caused a startle response in some cases, which resulted in incomplete inhalation. Under these conditions, patients unfamiliar with the device may discontinue inhalation and, therefore, not receive the full, intended dose. CDRH requests that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting.

You must address the following:

- a. A human factors validation report that includes:
 - i. A detailed analysis of use performance and subjective data;
 - ii. Evaluation and documentation of user performance, use errors and task failures
 - iii. An evaluation of the effectiveness of proposed mitigation strategies (training, device labeling, etc.) through simulated use scenarios;
 - iv. Discussion of how unanticipated failures can be handled; and
 - v. Discussion of any further mitigation strategies necessary and if further validation is necessary.
- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to safe use of the product. The study must evaluate feedback provided by test participants, which focuses on their ability to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
- c. You must conduct a thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients. This analysis should include the independent and integrated aspects of both the device and user interactions. The risk analysis should address whether the device is used in ways that were not anticipated, especially if the device use environment affects device utility and user comprehension. This risk analysis should also include a discussion of the mitigations against use-related risks, and it should evaluate the effectiveness of the mitigations, based on the human factors validation study results.

Evaluation of Sponsor's Response to HF Request

In the resubmission, the sponsor provided a red-line HF protocol based on previous correspondences/meetings with the Agency and the final HF validation study report.

Summary of Findings from HF Report

Intended device users, uses, use environments, and training

Staccato Loxapine has been developed for the treatment of agitation associated with schizophrenia or bipolar disorder in adults. The administration of *Staccato* Loxapine to patients is intended to be supervised by a healthcare provider (HCP) in a healthcare setting such as an emergency department of a hospital, an in-patient psychiatric ward, a psychiatric emergency service, or a psychiatrist's office.

HCPs would prepare the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients will only be responsible for following the HCP's instructions in order to actuate the device and inhale the drug. Patients will not be responsible for reviewing the instructions for use, for preparing the device, for determining when the device is ready to use, or for determining if the device has actuated.

A wide range of HCPs working in various clinical environments are expected to administer *Staccato* Loxapine. For example, users might include Registered Nurses (RNs), Licensed Practical Nurses (LPNs), and physicians working in general hospital units, emergency departments, and psychiatric units or clinics.

No training on the instructions for use is expected for these users prior to device use; however, the instructions are presented in both the Full Prescribing Information for the product and the pouch label.

Device user interface

The user interface consists of the following elements:

- A pull tab, which is used to prepare the product for use after being removed from the pouch
- An indicator light (a green LED) which indicates whether the device is ready to be used or has already been used
- A mouthpiece for the patient to put in their mouth and inhale through

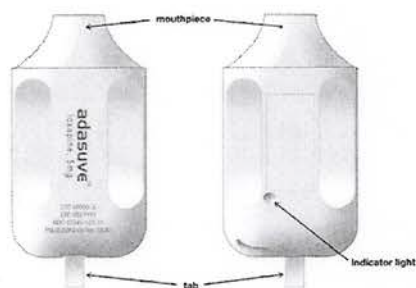


Figure 1. Images of the *Staccato* Loxapine device highlighting the user interface elements.

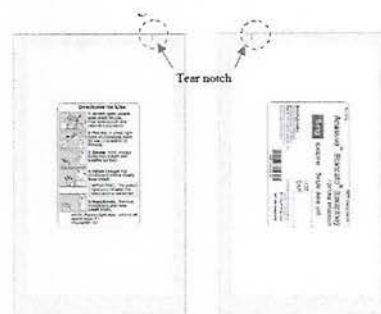


Figure 2. Images of the pouch for *Staccato* Loxapine. The tear notch is highlighted by the arrow pointing to the circle.

In addition to these elements on the device itself, the pouch has a tear-notch to facilitate opening the pouch and removing the device at the time of use. The pouch is illustrated below in Figure 3.

The use of *Staccato* Loxapine consists of the following operational steps:

- The HCP opens the pouch to remove the device
- The HCP removes the tab to activate the device for use and observes the illumination of the green LED indicator to confirm that the device is ready for use
- The HCP provides inhalation instructions to the patient
- The patient follows the inhalation instructions given by the HCP
- The HCP confirms the delivery of the dose by checking that the LED has turned off

Note that the HCP is the user primarily responsible for ensuring that the device is prepared properly and that the dose is administered properly. The patient is only responsible for following the HCP's instructions to actuate the device and inhale the drug. Instructions for use are provided with the device both as a part of the Full Prescribing Information and as a label on the back of the device pouch.

User task selection, characterization and prioritization

- Risk analysis methods
- Use-related hazardous situation and risk summary
- Critical tasks identified and included in HFE/UE validation tests

Summary of formative evaluations

Formative usability evaluations included studies to evaluate the device inhalation resistance (effort required to achieve a certain inhalation flow rate) and the actuation reliability of the device, along with an evaluation of published literature on the usability of similar devices. Other findings from the clinical studies indicated that having more than one attempt to actuate the device is not problematic, as there were occasional reports of subjects and patients attempting multiple inhalations. Feedback from the clinical development program was also informative for the product design.

Most of the usability-related observations made during the clinical studies indicated that the root causes were identified and corrected. Other observations were considered to be indicative of the following two potential use errors:

- Inadequate inhalation
- Failure to recognize use state

The potential harms related to inadequate inhalation are a missed or delayed dose, or underdose which all have a minor severity impact. The potential harms related to a failure to recognize use state are a missed dose, a delayed dose or inappropriate administration of a second dose (in the case of a failure to recognize that the first dose was delivered).

The sponsor indicated that harms related to a missed dose or delayed dose are minor in severity. Harms related to inappropriate administration of a second dose could potentially have a serious safety impact. However, in the course of the clinical development program, there were no

instances in which subjects received a second dose inappropriately. In addition, in consideration of the combination of potential harm and probability of occurrence for these potential use errors results in a level of risk that is considered acceptable.

Validation testing

The purpose of the testing was to validate the use-safety and usability of *Staccato* Loxapine and the associated Instructions for Use. Representative users (healthcare providers and patients) interacted with the device in a simulated-use environment. These environments were chosen so that "challenge scenarios" could be evaluated that might not occur naturally in a clinical study. In order to simulate the environmental aspects of a healthcare setting that could affect dose administration, ambient background noise typical for such a setting were present during the test sessions.

In the initial summative HF study, 15 HCPs, representative of the physicians and nurses were enrolled. For the patient arm of the study 16 non-agitated individuals with schizophrenia and 16 non-agitated individuals with bipolar disorder participated in the study. Both sets of representative patients were required to have been treated for agitation in a healthcare setting at least once in the past. This initial study identified modifications that needed to be made to the pouch and the IFU for the HCP. A supplemental HF study was conducted with another 15 HCPs to revalidate the changes.

The HCPs performed 10 tasks in the initial study and 6 directed tasks in the supplemental study, most of which involved scenarios that challenged HCPs' ability to direct use of the device (e.g. intentionally defective devices or non-compliant standard patients). The representative patients in the initial study participated in 5 directed tasks, each of which involved normal use of the device. Two distractions were introduced during the representative patient directed tasks to challenge their ability to follow the HCP directions during the distraction. These tasks were chosen to be representative of either previously observed issues in the clinic or potential issues identified in risk analyses and were intended to comprehensively assess the use-safety of the device.

Because the preparation and use of *Staccato* Loxapine involves several steps, each directed task for each participant consisted of a full dosing scenario, i.e., starting with preparing the device for use and finishing with dose administration. The exceptions to this are some of the "challenge" scenarios where intentionally defective devices were presented to HCPs.

(b) (4)

Discussion and implications for additional risk mitigation

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, Alexza has undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. They changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP were unaware to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

(b) (4)

While the Agency recognizes that Alexza has taken helpful measures in its effort to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that Alexza to take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Improvements should be demonstrated through focused HF/usability validation.

Recommendations

Please request Alexza to address the following concerns:

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, you have undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. You changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP were unaware to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

(b) (4)

While the Agency recognizes that you have taken helpful measures to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

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/s/

KIMBERLY S UPDEGRAFF

04/13/2012

Intercenter consult review entered into DARRTS for the CDRH review team.

**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**

Labeling and Human Factors Usability Study Review

Date: April 9, 2012

Reviewer: Yelena Maslov, Pharm.D., Acting team Leader
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPD, Deputy Director
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Adasuve (Loxapine) Inhalation Powder, 5 mg and 10 mg

Application Type/Number: NDA 022549

Applicant/sponsor: Alexza Pharmaceuticals

OSE RCM #: 2012-629

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

1 INTRODUCTION

This review evaluates Additional Summative Usability Study and Instructions for Use Labeling for Adasuve Inhalation Solution submitted in response to DMEPA's comments to the Applicant in OSE Review #2010-287, dated November 10, 2011.

1.1 REGULATORY HISTORY

The Applicant originally submitted Summative Usability Study, Supplemental Summative Usability Study, description of the device's design, and Instructions for Use (IFU) labeling on August 4, 2011. DMEPA made recommendations to the device design and Instructions for Use in OSE Review #2010-287, dated November 10, 2011. Additionally, DMEPA and CDRH recommended re-testing the device and the IFU through the Usability Study similar to the ones submitted to the Agency on August 4, 2011 after additional device modifications and revisions to the IFU were implemented to ensure the device can be used safely according to the labeling and does not introduce potential for additional errors. Subsequently, on March 8, 2012 the Applicant submitted Additional Summative Usability Study conducted to validate the changes to the device and IFU per DMEPA's recommendations.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 4, 2011 NDA submission.

- Active Ingredient: Loxapine
- Indication of Use: Rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults.
- Route of Administration: Oral Inhalation
- Dosage Form: Inhalation Powder
- Strengths: 5 mg and 10 mg
- Dose and Frequency: 5 mg or 10 mg once in 24 hours
- How Supplied: The device is packaged in a foil pouch and each carton contains five units of the product.
- Storage: Room temperature between 15°C and 30°C (59°F and 86°F)
- Container and Closure Systems: Inhalation Device

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Description and illustration of the device submitted on March 8, 2012 (Appendix A)
- Instructions for Use (IFU) Labeling submitted on March 8, 2012 (Appendix B)
- Additional Summative Usability Study for Adasuve submitted on March 8, 2012 (See Appendix C for the summary of the study)
- Use FMEA for Adasuve submitted on March 8, 2012 (no image)

We evaluated the results of the Usability Study, the device design, and the IFU labeling based on our evaluation of the results of the Usability Studies, comments from the participants, and the root cause analysis from the test administrators (b) (4)

3 RESULTS AND DISCUSSION

The following section discusses the findings of DMEPA's evaluation of the Additional Usability Study, IFU, and device design.

3.1 ADDITIONAL SUMMATIVE USABILITY STUDY FOR ADASUVE

- The Applicant completed an Additional Summative Usability Study based on recommendations from DMEPA and CDRH, after implementing revisions to the IFU and device design per DMEPA's recommendations in OSE Review #2010-287.
- The majority of issues identified in the previous Summative Usability Study and Supplemental Summative Usability Study (i.e. forgetting to check LED light to ensure activation or delivery of the product and instructing patients to hold their breath) have been eliminated or significantly reduced after revisions to the IFU and device have been implemented. However, a few user errors relating to forgetting to check the LED light to ensure activation, functioning to instruct patients to exhale, or instructing patients to hold their breath have occurred.
 - a. Forgetting to check the LED light occurred with 2 participants that did not notice that LED did not turn on during challenge scenario (i.e., defective device was given to participants that did not activate and LED light was off after tab was pulled). However, both of the participants ensured that the LED light turned on during the remaining five scenarios. The test administrator determined that the root cause of this error was nervousness and preoccupation of participants. This error can result in dose omission, which can potentially lead to failure to relieve symptoms of agitation. Although 2 of the 15 participants did not check the LED light to ensure the activation of the device during this usability study, this type of error was significantly reduced from the previous usability studies (i.e. this error occurred twice, in which the device "malfunctioned" vs. over 20 times in a previous study). As a result, it appears that the revisions to the device and the IFU represented effective means in minimizing this type of error.

- b. Forgetting to instruct patients to exhale occurred with 6 participants on 8 occasions. HCP participants did not direct patients to exhale prior to inhaling during challenge scenarios when HCPs needed to re-instruct the patient to exhale prior to inhaling on 8 occasions with 6 participants. The majority of participants stated that they assumed the patient will exhale on their own prior to inhaling since they instructed the patient to exhale the first time. One participant stated that she forgot to tell patient to exhale. This error may result in the inhalation of the partial dose if the inhalation is not forceful enough to obtain the full dose from the inhaler. However, if a partial dose is administered, the LED light will remain on, which along with the IFU should prompt the healthcare provider (HCP) to direct the patient to inhale Adasuve from the device again. As a result, although this error may occur with this device, the IFU labeling contains a clear step referring the HCP to direct the patient to exhale. Additionally, this error is inherent to the inhalation devices. Thus, no additional changes to the labeling or device are warranted at this time.
- c. Forgetting to instruct patient to hold breath occurred on one occasion. A participant did not direct the patient to hold her breath after inhalation of the product. The test administrators determined the root cause for this error was the participant's pre-occupation with checking the LED light. The participant directed the patient to hold breath during the remaining tasks. This type of error may lead to underdose of the product; and thus, failure to relieve symptoms of agitation. Although this error occurred once during usability study, it was significantly reduced from the previous usability study (i.e., once vs. over 20 times). Additionally, an IFU contains a clear step with an illustration referring the HCP to direct the patient to hold their breath. Thus, no additional changes to the labeling or device are warranted at this time.
- HCPs will be unfamiliar with this unique product, and as such the Applicant should develop a communication plan to educate HCP regarding the correct use of the product through in service education sessions and promotional materials.

3.2 DEVICE DESIGN

The revised device addressed DMEPA's previous concerns by implementing all DMEPA's recommendations per OSE Review #2010-287. Thus, we have no further recommendations for the device design.

3.3 INSTRUCTIONS FOR USE LABELING

- The Applicant addressed all of the DMEPA's recommendations per OSE Review #2010-287.

-  (b) (4)

(b) (4)
Thus, this statement should be revised for clarity and to ensure it is not overlooked.

- (b) (4)
Thus, the IFU should be revised to ensure this important safety information is stated.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the device design did not identify any additional areas of improvement. However, based on new safety information concerning bronchospasm and the participants' recommendation from the additional Summative Usability Study, our evaluation of the IFU labeling identified additional areas prone to vulnerabilities that should be improved upon prior to marketing. Thus, Section 4.1, *Comments to the Applicant*, contains our recommendations regarding the IFU labeling.

If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

4.1 COMMENTS TO THE APPLICANT

A. Instructions for Use (IFU)

- Add a step prior to the Heading "Instruct patients to:" as follows:

Step 3: Explain Procedures to Patient:

Explain administration procedure to patients prior to the procedures and let patients know it is important to follow the instructions. Advise patients that the inhaler may produce a flash of light or a clicking sound, or become warm during use. These are normal.

We request an addition of this step to ensure the healthcare providers inform the patients of the administration procedure prior to using the inhaler.

- Delete the statement (b) (4)
This information is repetitive to the added step.
- Ensure you revise the step numbers and you reference the correct step number throughout the IFU.
- Revise the statement (b) (4)

"Important: If the green light stays on after the patient inhales, the dose has NOT been delivered. Instruct the patient to repeat Steps 4, 5 and 6 up to 2 additional times".

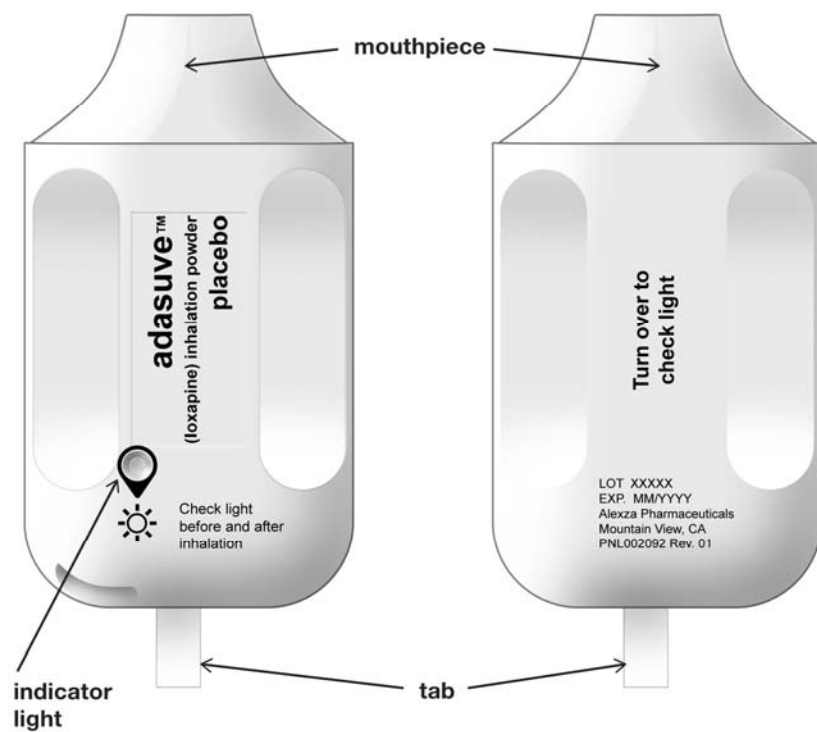
We recommend this revision because this statement was overlooked or misinterpreted by two study participants. (b) (4)

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
 - [REDACTED] (b) (4)
 - [REDACTED] (b) (4)
 - Include [REDACTED] (b) (4) as follows:

“Monitor patients 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”.
- Ensure you include five Instructions for Use in the Kit and attach it to each pouch containing Adasuve.

APPENDICES

Appendix A: Device Design



3 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix C: Summary of the Additional Usability Study for Adasuve

- Only healthcare practitioners were enrolled.
- 15 Healthcare professionals (10 nurses and 5 physicians). The healthcare professionals work in psychiatric environment (e.g., hospitals in-units, outpatient clinics, private practice) and emergency departments.
- Healthcare practitioners interacted with “actor” patients that pretend to be agitated to provide consistent patient interactions.
- Test environment included noise similar to the healthcare setting noise: played soundtrack of footsteps, conversations, cabinets opening and closing, rolling carts, beeps of medical devices, telephone ringing.
- One healthcare practitioner task was considered to prepare the device for use while using IFU and direct the “actor” patient to use the device.
- The healthcare practitioners had to perform this task 6 times in randomized order. Three times the healthcare practitioner had to perform task under “normal” conditions (i.e., no product quality issues or distractions) and three times healthcare practitioner had to perform a task when the device was purposefully adjusted to malfunction (i.e., LED light not turning on or off) or “actor” patient exhaled into the device instead of inhaling.
- After the test was administered, the test administrators asked the health care practitioners open-ended and closed-ended questions regarding the use of the device and the steps that healthcare practitioners might have failed. Based on the responses and through observations, root causes were identified by the test administrators.

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/s/

YELENA L MASLOV
04/09/2012

KELLIE A TAYLOR
04/09/2012

CAROL A HOLQUIST
04/09/2012



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: March 26, 2012 **Date Consulted:** February 6, 2012

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Psychiatry Products (DPP)

Drug: Adasuve (loxapine) NDA 022549

Subject: NDA Resubmission

Sponsor: Alexza Pharmaceuticals, Inc.

Materials Reviewed: Adasuve product labeling and Resubmission materials

Consult Question: DPP would appreciate input from PMHS regarding the proposed labeling for this application (particularly section 8).

INTRODUCTION

Alexza Pharmaceuticals Inc. (Alexza) submitted a New Drug Application, NDA 022-549 for Loxapine Inhalation Powder on December 11, 2009 with the proposed indication of rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults. A Complete Response (CR) letter was issued to the sponsor on October 8, 2010, citing clinical (pulmonary toxicity), quality, device (human use validation) and facility inspection deficiencies. On August 4, 2011, Alexza resubmitted NDA 022-549 for Adasuve (loxapine) Inhalation Powder, indicated for the acute treatment of agitation associated with Schizophrenia or Bipolar I Disorder in adults. The product is a single-use, hand-held, drug-device combination and is a new dosage form of loxapine, which was approved in the United States (US) in 1975. As part of the resubmission, the sponsor included a Risk Evaluation and Mitigation Strategy (REMS) program which limits the use of Adasuve to use only in enrolled health care facilities and only for administration to patients within those facilities, in an effort to mitigate the risk of bronchospasm in patients. On January 12, 2012, the sponsor submitted a REMS amendment to the CR, extending the review period and based on the outcome of a Psychopharmacologic Advisory Committee (PDAC) on December 12, 2011, the sponsor submitted a labeling amendment incorporating PDAC concerns, including limiting the product to one dose per 24 hours. The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on February 6, 2012 requesting input regarding proposed labeling for Adasuve, in particular, Section 8 of labeling.

BACKGROUND

Schizophrenia and Pregnancy

Schizophrenia is a neuropsychiatric disease, affecting approximately 1% to 2% of the population. Antipsychotic medications are commonly prescribed for schizophrenia, which can be a complex and debilitating disease. The age of onset of the disease is during the peak of reproductive potential for women and approximately 60% of women with a psychiatric disorder will have children. Schizophrenia has been associated with adverse pregnancy outcomes and treatment during pregnancy is necessary for women who have pre-existing illness, exacerbations or who develop illness, balanced with the effects of treatment on the fetus^{1,2}. Loxapine is one consideration for treatment or management of schizophrenia during pregnancy³.

Loxapine

Loxapine, a dibenzoxazepine derivative, is a typical antipsychotic medication used for treatment of acute or chronic schizophrenia⁴. It was originally approved in the United States (US) in 1975, and is available orally for chronic disease management. An intramuscular (IM) dosage form, was available for acute management of symptoms, however, is no longer marketed. Alexza's application for Adasuve Inhalation Powder would provide non-invasive, acute treatment ability.

¹ Einarsen A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. *Journal of Psychiatric Practice* 2009;15(3):183-192.

² Sivertz K, Kostaras X. The use of psychotropic medications in pregnancy and lactation. *BC Medical Journal* 2005;47(3):135-138.

³ Sivertz K, Kostaras X. The use of psychotropic medications in pregnancy and lactation. *BC Medical Journal* 2005;47(3):135-138.

⁴ Heel RC, Brogden RN, Speight TM, Avery GS. Loxapine: a review of its pharmacological properties and therapeutic efficacy as an antipsychotic agent. *Drugs* 1978;15:198-217.

In animal studies, loxapine was not teratogenic or embryotoxic and there are no studies of loxapine use during pregnancy⁵. One author cited manufacturer reported outcomes of three pregnancies with exposure to loxapine; one infant with achondroplasia, one infant with multiple unspecified malformations and one infant with tremors at 15 weeks (with exposure throughout pregnancy)⁶. These reports are retrospective, and are without other descriptive data. On February 22, 2011, the Food and Drug Administration (FDA) published a Drug Safety Communication regarding the updating of antipsychotic drug labels on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. The FDA identified 69 reports of cases of neonatal extrapyramidal signs (EPS) or withdrawal associated with antipsychotic drugs from the Adverse Event Reporting System (AERS) database. The pregnancy section of labeling was updated for the antipsychotic drug class with information about the potential risk for EPS and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy⁷.

Regarding human lactation, loxapine can elevate serum prolactin levels, however, there are no data available on use of loxapine during breastfeeding⁸.

REVIEW OF SUBMITTED MATERIAL

Sponsor's Submitted Proposed Adasuve Labeling (Appendix A)

A copy of the sponsor's proposed labeling can be found in Appendix A of this review.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

PMHS-MHT labeling recommendations (label excerpts) appear below. **Appendix B** of this review provides a tracked-changes version of labeling that highlights the recommended PMHS-MHT revisions.

⁵ Website: <http://www.reprotox.org/Default.aspx>. REPROTOX February 2012.

⁶ Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. *Journal of Psychiatric Practice* 2009;15(3):183-192.

⁷ Website: <http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm>. FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. February 2011.

⁸ Website: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~Q4XWG6:1>. National Library of Medicine LactMed Database. March 2012.

MHT Labeling Recommendations (label excerpts provided):

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother.
(8.3)

Reviewer Comment:

Revised to provide required regulatory language for pregnancy category C drugs and for nursing mothers.

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of Adasuve use in pregnant women. Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Adasuve was not teratogenic or embryotoxic in animal developmental reproductive studies. Adasuve has demonstrated developmental delays, increased perinatal and neonatal deaths in rat offspring exposed to Adasuve when given in doses approximately 0.5 and 2 times the maximum recommended human dose. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Animal Data

No embryotoxicity or teratogenicity was observed in studies in rats at oral doses up to 12 mg/kg (approximately 12 times the maximum recommended human dose of 10 mg/day on a mg/m² basis), in rabbits at oral doses up to 60 mg/kg (approximately 120 times the maximum recommended human dose of 10 mg/day on a mg/m² basis), or in dogs at oral doses up to 10 mg/kg (approximately 32 times the maximum recommended human dose of 10 mg/day on a mg/m² basis). Perinatal studies have demonstrated developmental delay (reduced weights, delayed ossification, and/or distended renal pelvis with reduced or absent papillae) as well as increased numbers of perinatal and neonatal deaths in offspring of rats treated from mid-pregnancy with oral doses of 0.6 and 1.8 mg/kg (approximately 0.5 and 2 times the maximum recommended human dose of 10 mg/day on a mg/m² basis, respectively).

Reviewer Comment:

The Pregnancy section was restructured and sub-headers (Risk Summary, Animal Data) were added to provide and organized presentation of data. The Risk Summary paragraph provides the appropriate regulatory language and a summary of risks, based on the available data, followed by the animal data. The FDA required labeling language regarding the use of antipsychotics during pregnancy and the risks to neonates appears under the Human Data sub-header.

8.3 Nursing Mothers

It is not known whether Adasuve is present in human milk. Loxapine and its metabolites are present in the milk of lactating dogs. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Adasuve, a decision should be made whether to discontinue nursing or discontinue Adasuve, taking in to account the importance of the drug to the mother.

Reviewer Comment:

The Nursing Mothers section was restructured, providing appropriate regulatory language, stating that it is not known if Adasuve is present in human milk, however, because of the potential risk if present, a decision to discontinue drug or discontinue breastfeeding should be made. As this formulation of loxapine is indicated as an acute treatment, it may be acceptable to provide instructions regarding pumping and discarding breastmilk, should a breastfeeding mother wish to continue breastfeeding. The MHT would like to discuss this option with the Division, regarding feasibility, and the MHT would make the appropriate language changes, should this option be preferred.

17 PATIENT COUNSELING INFORMATION

Pregnancy

- Advise female patients of reproductive potential that neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery and to inform their healthcare provider if they are pregnant or become pregnant while taking Adasuve [see Use In Specific Populations (8.1)].

Nursing Mothers

- Advise female patients of the potential for serious adverse reactions in nursing infants from Adasuve and to inform their healthcare provider if they are breastfeeding or plan to breastfeed while taking Adasuve [see Use In Specific Populations (8.3)].

Reviewer Comment:

Section 17, Patient Counseling Information provides detailed instructions for health care providers should provide to patients regarding safe use of a drug. Information is presented in bulleted format, stating the risks and counseling to provide to patient regarding the risks. Counseling and advice should be provided to female patients of reproductive potential regarding the potential risk to neonates if Adasuve is used during pregnancy and breastfeeding.

Appendix A- Sponsor's Submitted Proposed Adasuve Labeling

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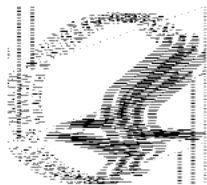
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/s/

TAMMIE B BRENT HOWARD
03/26/2012

MELISSA S TASSINARI
03/26/2012

LISA L MATHIS
03/27/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Pediatric Labeling Review

Date: March 12, 2012 **Date Consulted:** February 6, 2012

From: Erica Radden, M.D., Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lisa Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Psychiatry Products

Drug: Adasuve (loxapine)

Application number: NDA 22-549 (IND 73,248)

Submission date: January 12, 2012 (Labeling)
August 4, 2011 (Complete Response)

Sequence number: 0031, 0026
<\\CDSESUB1\EVSPROD\NDA022549\022549.enx>

Sponsor: Alexza Pharmaceuticals

Subject: Pediatric Use Labeling

Consult question: “DPP would appreciate input from PMHS regarding the proposed labeling for this application (particularly Section 8).”

Materials Reviewed:

- Draft loxapine Labeling, submitted January 12, 2012
- PREA Waiver Request, submitted September 30, 2009

- Resubmission of NDA (August 4, 2011)
- PeRC PREA Subcommittee Meeting Minutes (August 11, 2010)
- Summary of Clinical Safety
- Complete Response letter (October 8, 2010)

BACKGROUND

On December 11, 2009, Alexza Pharmaceuticals submitted a New Drug Application for Staccato® loxapine for Inhalation (*Staccato* loxapine or Adasuve), an antipsychotic, indicated for the rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults. Adasuve inhalation powder is a drug-device combination and represents a new dosage form for loxapine as an aerosol (b) (4)

If approved, Adasuve would be the first inhaled form of an antipsychotic with this indication; there are three approved intramuscular forms (Zyprexa, Geodon and Abilify). Oral loxapine succinate is approved for the treatment of schizophrenia in adults and IM loxapine hydrochloride, which is no longer marketed, was approved for the management of schizophrenia.

Reviewer comment: The Sponsor's background package states that IM loxapine is approved for the treatment of acute agitation. Although a copy of approved labeling was not found in DARRTS, a document regarding the medical necessity of the product states the indication is "schizophrenia" with no important off label uses noted¹

Adasuve is being submitted as a 505 (b)(2) new drug application. Loxapine is also being developed for the treatment of migraine headache, (b) (4)

The Staccato delivery mechanism is a proprietary agent of Alexza Pharmaceuticals for other single-dose drug products as well.

The division issued a Complete Response (CR) letter on October 8, 2010, citing pulmonary toxicity as the primary clinical safety concern. Clinically significant decreases in FEV1 were noted (greater than 10-20%). In healthy subjects, there was a decrease in FEV1 >10% in 27% of the loxapine group and 27% of the placebo group suggesting that the device itself may be contributing to the observed pulmonary toxicity. Decreased pulmonary function was particularly evident in patients with a history of asthma and COPD where the decrease in FEV1 was 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. Additionally, an increased number of adverse respiratory events (58-69%) occurred in subjects with asthma and COPD. The severity of pulmonary toxicity was also noted to be dose related as greater decreases in FEV1 compared to their first dose was noted after treatment with a second dose. FEV1 did not return to baseline 24 hours post-dose. The letter noted concern that even with a risk evaluation and mitigation strategy (REMS), a reasonable degree of safe use with this product in the intended population may not be possible. In addition to gathering more information about the pulmonary toxicity, there were also device-related and chemistry and manufacturing issues

¹ Medical necessity letter, dated June 30, 2004 in NDA 018039 (IM Loxitane (loxapine HCl))

Following an End of Review meeting with the division on December 17, 2010 and a Type C Meeting on April 29, 2011, Alexza Pharmaceuticals submitted a Complete Response on August 4, 2011 to address the pulmonary toxicity safety concerns. A Boxed Warning describing the risk of bronchospasm as well as a Contraindication for patients with acute respiratory signs/symptoms such as wheezing or those taking asthma or COPD medications was included. An updated draft labeling and a comprehensive REMS package which included a Medication Guide, a multi-component Communication Plan, and an Element to Assure Safe Use (ETASU) ensure the product would only be available in enrolled healthcare facilities that would have the capabilities to treat acute bronchospasm were proposed. Finally, a synopsis for a large Phase 4 observational study to obtain information on post-marketing information with respect to the risk of bronchospasm and real-world use patterns in medical or psychiatric emergency settings was provided. Additionally, a human factors validation program was conducted to ensure the product could be used effectively in the proposed clinical setting, and issues related to the device and chemistry and manufacturing were addressed.

The application was presented to a Psychopharmacologic Advisory Committee (PDAC) on December 12, 2011. The panel members provided feedback regarding labeling to limit the drug use to one dose per 24 hours, and also believed that a REMS with ETASU would be required. A REMS amendment was submitted on January 10, 2012 and updated labeling was submitted on January 12, 2012. The division now feels that the safety concerns will be adequately addressed by the proposed safety precautions in the labeling and REMS package

PREA Requirements

The Pediatric Research Equity Act (PREA) requires pediatric studies to assess safety and efficacy, and to support dosing and administration of a drug or biological product when approval is sought for a new active ingredient, indication, dosage form, dosing regimen or route of administration. This new indication (presuming the IM product is not indicated for agitation in schizophrenia and bipolar disorder), dosage form and route of administration trigger PREA. Adasuve (*Staccato* loxapine) has not been evaluated in pediatric patients. In accordance with the PREA, the Sponsor has submitted a partial waiver request of studies of children under age 10 with bipolar disorder and (b) (4) with schizophrenia as necessary studies are impossible or highly impractical because the number of pediatric patients in this age group is so small (section 505B(a)(4)(B)(i) of the Act). (b) (4)

The sponsor also requested a deferral of pediatric studies for adolescents with schizophrenia aged (b) (4)-17 years, and children and adolescents with bipolar disorder aged 10-17 years citing the following reasons: (1) The drug product is ready for approval for

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/s/

ERICA D RADDEN
03/16/2012

HARI C SACHS
03/16/2012
I agree with the recommendations in this consult.

LISA L MATHIS
03/19/2012



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Ave
Silver Spring, MD 20993

NDA 022549**Response to Consult Request**

Date: March 5, 2012
From: Nayan Patel, Biomedical Engineer, Anesthesiology and Respiratory Device Branch,
Division of Anesthesiology (ARDB), General Hospital, Infection Control, and Dental
(DAGID), CDRH
Through: Sugato De, M.S. Combination Products Team Lead, DAGID/ODE/CDRH
Lex Schultheis, M.D., Ph.D, ARDB Chief, DAGID/ODE/CDRH
Kwame Ulmer, M.S. Deputy Division Director, Science and Policy, DAGID/ODE/CDRH
To: David Claffey, Ph.D, Division of Psychiatry Products, CDER
Kimberly Undegraff, RPh, MS, RAC, Senior Regulatory Project Manager
Thomas Laughren, M.D., Division Director, Division of Psychiatry Products, CDER
Re: NDA 022549 Alexza Staccato Loxapine for Treatment of Agitation

I. Summary

We have reviewed the updated labeling information pertaining to the device component of this submission.

Please request the sponsor provide additional information in the device labeling as per the recommendation section below.

II. Purpose of Consult

The Division of Psychiatry Products (CDER) has requested a consult from CDRH regarding the review of an NDA submission, # 022,549, Staccato Loxapine manufactured by Alexza Pharmaceuticals, Inc. This is a review of the updated labeling the sponsor provided on January 12, 2012.

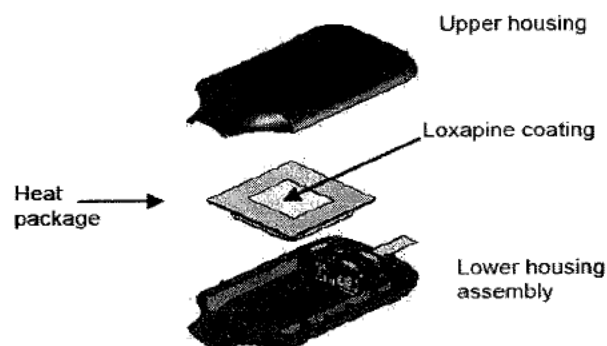
III. Device Description

Staccato® Loxapine for Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg.

Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza. Oral inhalation through the 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 rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

Staccato Loxapine (5 mg and 10 mg) has been developed 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.

Figure 1. Schematic of *Staccato* Loxapine



Note: Pouch not shown in schematic. (b) (4) are processing aids that are evaporated during drug product manufacturing.

(Figure 1: Sponsor Document, Original Application, Sequence 0000, m3.2.P.1 Description and Composition of the Drug Product, page 2)

IV. Intended Use

The proposed combination product is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder.

V. Discussion

The sponsor had provided updated labeling to CDER in response to Psychopharmacologic Drugs Advisory Committee Meeting (PDAC) held on 12 December 2011 at which Alexza agreed to revise the proposed Adasuve REMS based on Agency recommendations and to limit treatment with Adasuve to 1 dose per 24 hour period. Reference is also made to an Information Request (03 December 2011) which included Agency recommendations for changes to the Instructions for Use (to be tested as part of Human Factors validation).

The labeling text provided has been updated to incorporate changes to the REMS, dosing recommendations, and Instructions for Use.

The updated device labeling provided by the sponsor is adequate. However, we recommend the sponsor provide additional information regarding the device performance specifications in the device labeling.

VI. Recommendation

Please request Alexza to address the following regarding their device labeling:

The Agency believes that your device labeling is an essential component in communicating the dosing specifications of the device. Accordingly, please include the particle specifications that you have established in your performance testing for the drug, including mass-median aerosol diameter (MMAD), total delivered dose, total respirable dose, respirable fraction and geometric standard deviation (GSD). For each of the specifications identified above, please include the range of measurements observed in your performance tests and provide the corresponding standard deviation. We recommend that you characterize particle size using three categories: course particles (>4.7 microns), fine particles (<4.7 microns), and extra-fine particles (<1 micron). As a function of the total dose delivered, please include specifications for the total mass and the fraction of each of these size ranges. Please note that each of the specifications listed in the labeling should be shown to have an appropriate level of statistical confidence as demonstrated by your performance tests.



Nayan Patel, Reviewer

3/5/12


Date



Sugato De, Combination Products Team Lead

3/5/12


Date



Lex Schultheis, Branch Chief

3/5/12

Date



Kwame Ulmer, Deputy Division Director

3/5/12

Date

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/s/

KIMBERLY S UPDEGRAFF

03/19/2012

Intercenter consult review from CDRH (labeling)

**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**

Label and Labeling Review

Date: March 12, 2012

Reviewer: Yelena Maslov, Pharm.D., Acting Team Leader
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Adasuve (Loxapine) Inhalation Powder, 5 mg and 10 mg

Application Type/Number: NDA 022549

Applicant/sponsor: Alexza Pharmaceuticals

OSE RCM #: 2010-87-1

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

1 INTRODUCTION

This review is written in response to the Division of Risk Management request to emphasize the important safety information related to respiratory conditions by addition of relevant statements to the pouch and carton labeling.

1.1 BACKGROUND

DMEPA previously completed Usability Study, Label, and Labeling Review for Adasuve on November 10, 2011. However, during January 24, 2012, internal Adasuve labeling meeting, the Division of Risk Management (DRISK) proposed to add contraindication statement related to the signs and symptoms of respiratory disease (i.e., asthma or COPD) reminder to the pouch and carton labeling to emphasize this important safety information.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Device Labels submitted on August 24, 2011 (See Appendix A)
- Foil Pouch Labeling submitted on August 24, 2011 (See Appendix A)
- Carton Labeling submitted on August 24, 2011 (See Appendix A)

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA agrees with DRISK recommendations. This is an important safety information since administration of this product to a patient with a compromised lung function may lead to bronchospasm and possibly, death.

Thus, due to safety concerns, DMEPA revised recommendations to the pouch and carton labeling to include relevant statements regarding contraindication and monitoring parameters. Additionally, for the purposes of keeping all the recommendations to the Applicant together, we included recommendations for the device label from previous OSE Review #2010-287. Thus, Section 3.1, *Comments to the Applicant*, contains recommendations regarding device label, pouch and carton labeling.

3.1 COMMENTS TO THE APPLICANT

A. Device Label

1. Include the dosage form immediately following the established name, followed by the strength [i.e. (loxapine) inhalation powder, 10 mg]. The proprietary and established names, dosage form, and strength should be relocated to the side of the device that has the LED light. The lot number, expiration date, NDC, and PNL numbers can remain on the opposite side.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. Per 21 CFR 201.10(g)(1), include brackets around the established name so that the relationship between the proprietary name and established name is clear.
3. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
4. Per 21 CFR 201.10(i)(iv), include the name of the manufacturer, packer, or distributor on the opposite side of the LED light.
5. Per 201.100 (b)(2) include the route of administration if space permits.

B. Foil Pouch Labeling (Front Side)

1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and has the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Increase the prominence of the proprietary and established names as they should be the most prominent information on the label. Currently, they can be overlooked by other information on the label.
3. Present the proprietary name followed by the established name immediately followed by the dosage form then the strength. Present in the following manner:

Adasuve
(loxapine) inhalation powder
xx mg

4. Remove “loxapine” following the strength as the established name is already included following the proprietary name and as it crowds the label.
5. Include a space between the number and the unit in the presentation of the strength (i.e. 5 mg rather than 5mg).
6. Include the statement “Discard after one use” following the single dose unit statement.
7. Add the following prominent statement to the principle display panel “Adasuve is contraindicated in patients with acute respiratory signs/symptoms (e.g., wheezing) or who are taking medications to treat asthma or COPD.” This important statement to serve as a reminder to healthcare practitioners not to administer Adasuve to patients with active airway disease. In order to accommodate placement of this statement to the principle display panel without overcrowding the panel, please minimize the prominence of the following information:
 - Manufacturer information
 - Storage information
 - PNL number and revision date
 - Lot Number and Expiration Date

8. Delete one of the NDC numbers as there are two of them printed on the principle display panel.
9. Consider additional differentiation between 5 mg and 10 mg strength of the Adasuve through additional use of color, boxing, or some other means. Presently, labeling for both strengths appear similar to each other for the exception of the colored strengths, which can lead to selection of the wrong strength.
10. Per 21 CFR 201.100(b)(2) or 201.55, include the usual dosage statement.
11. Per 21 CFR 201.100(b)(3), include the route of administration.
12. Delete the statement (b) (4) as this statement crowds the label and does not represent a critical step in the correct administration of Adasuve.
13. Decrease the prominence of the “Rx Only” statement by relocating it to a less prominent position of the label.

D. Carton Labeling

1. See comments B.1 through B. 9 and revise the carton labeling accordingly.
2. Increase the prominence of the route of administration by using bigger font type or bolding as this important information may be overlooked because it appears in the same font size as other information on the label such as storage temperature.
3. Decrease the “Rx Only” statement by decreasing the font size as this statement completes with the most important information on the label such as proprietary and established name, dosage form, and strength. same

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/s/

YELENA L MASLOV
03/12/2012

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 14, 2011

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: December 12, 2011 Meeting of the Psychopharmacologic Drugs Advisory Committee

TO: Members, Psychopharmacologic Drugs Advisory Committee (PDAC)

This one-day meeting of the PDAC will focus on safety and efficacy issues for NDA 22-549, an application for Staccato Loxapine for Inhalation, for the treatment of agitation associated with schizophrenia and bipolar disorder.

Initial NDA

Loxapine is a first generation antipsychotic (primarily D2 antagonism) approved since 1975 for the treatment of schizophrenia. Staccato Loxapine for Inhalation is a single-use, hand-held drug device combination product intended to provide for rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. Oral inhalation through the Staccato device triggers the controlled rapid heating of a thin film of loxapine to form a drug vapor which is then inhaled. The vapor condenses to aerosol sized particles for delivery to the deep lung, with expectation of rapid systemic delivery. This new dosage form is intended to be used for the treatment of agitation associated with schizophrenia and bipolar disorder. Three intramuscular forms of atypical antipsychotics are approved for this indication in the US (Zyprexa, Geodon, and Abilify). Staccato Loxapine, if approved, would be the first inhaled form of an antipsychotic for this use.

This application was first submitted to FDA on 12-11-09, and a Complete Response (CR) letter was issued on 10-08-10. FDA's review of this application resulted in a consensus view that, although the sponsor had demonstrated the efficacy of this product for the intended claim, the sponsor had not demonstrated its reasonable safety for the intended use. The safety concern was pulmonary toxicity, particularly in patients with asthma or COPD. The CR letter raised the concern that, even with a risk evaluation and mitigation strategy (REMS) to address this concern, it still might not be possible to provide for the safe use of this product.

The CR letter also detailed other deficiencies that would need to be addressed before the agency could complete its review of this application:

- The Center for Devices and Radiological Health (CDRH) requested the following:
 - A human factors study to assess usability of the product in settings involving representative providers and patients
 - A response to questions about achieving a better understanding of the basis for the observed airway reactivity
 - The conduct of a more realistic worst case simulation test
- The Office of New Drugs Quality Assessment (ONDQA) requested responses to a number of questions about the chemistry and manufacturing of this product

Response to CR Letter and Background Materials for PDAC

The sponsor responded to the CR letter with a 8-04-11 submission that attempted to address all of the above concerns. The background package for the committee includes selected reviews of the original application and of the response to the CR letter, as follows:

- Original application:
 - Division director review of original application--Thomas Laughren
 - Team leader review of original application--Robert Levin
 - CR letter for original application
 - Clinical review of original application--Frank Becker
 - Statistical review of original application--Yeh-Fong Chen
 - Pulmonary toxicity review--Anya Harry
- Response to CR action:
 - Division director memo to PDAC--Thomas Laughren
 - Clinical review--Frank Becker
 - Pulmonary toxicity review--Theresa Michelle
 - CDRH review, including review of device characteristics (Nayan Patel) and review of human factors (QuynhNhu Nguyen)
 - Office of Surveillance and Epidemiology reviews, including review of proposed post-marketing observational study (Cary Parker from the Division of Epidemiology I) and review of Risk Evaluation and Mitigation Strategy (REMS)[Kim Lehrfeld from the Division of Risk Management (DRISK)]
 - DMEPA review of product usability (Yelena Maslov)

Update on Status of Application

The Division of Psychiatry Products (DPP) continues to view the effectiveness of this product for the claimed indication to have been established. In addition, although we will have some recommendations, DPP has concluded that remaining issues regarding chemistry and manufacturing, and issues regarding engineering aspects of the device and human factors concerns have been adequately addressed. The primary issue that still needs resolution is the concern about a potential for pulmonary toxicity with this product in certain vulnerable populations. The sponsor has proposed a REMS to address this concern, however, FDA remains concerned about the adequacy of this program to allow for the safe use of this product.

Planned Presentations by FDA Staff

- Clinical background by Frank Becker from DPP
- Pulmonary toxicity by Theresa Michelle from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
- A discussion of the proposed REMS by Kim Lehrfeld from DRISK

Issues for Committee Discussion

Patients experiencing exacerbations of schizophrenia or bipolar mania often present with agitation that is important to address before patients can be transitioned to oral medications. Staccato Loxapine for Inhalation is intended as a treatment for agitation in these disorders, and DPP has concluded that the effectiveness of this product for this indication has been established. What has not yet been established, however, is how this product compares in effectiveness to the 3 intramuscular forms of atypical antipsychotics that are already approved for this indication in the US. Although the sponsor has provided some cross study comparisons to try to make the case that Staccato Loxapine for Inhalation may work faster than these other products, there has not yet been a head-to-head comparison of Staccato Loxapine with these other products, either alone, or in combination with benzodiazepines, as these products are often used in practice. [Note: Such combinations are off-label practices.] A major concern for this product is that it poses a significant risk of bronchospasm, particularly in patients with pre-existing airway disease, such as asthma and COPD. The sponsor has proposed a boxed warning to alert prescribers to this risk, and also a REMS to allow for the screening of patients at risk and for the safe management of patients who receive this treatment. They have also proposed a post-marketing observational study intended to compare the risks of pulmonary toxicity of this product with other products used for managing agitation in patients with schizophrenia and bipolar disorder.

Ultimately, we will be asking the committee to vote on one essential question:

“Has Staccato Loxapine for Inhalation been shown to be sufficiently effective as a treatment for agitation in patients with schizophrenia or bipolar mania, given its unique risks, and has it been shown to be reasonably safe for use in this context, when used in conjunction with the REMs that has been proposed by the sponsor, to justify its approval.”

In preparation for this central question we will want the committee to fully discuss several issues:

- Given the pulmonary risks that are unique to this product, how does its demonstrated efficacy compare with that of other products approved for this indication. Making such a comparison is admittedly challenging since a head-to-head comparison has not been made.
- Does the sponsor’s proposed REMS make it possible to use this product in a reasonably safe manner?
- Is the REMS even more burdensome than it needs to be, given any potential advantages of this product?

- If, after considering these issues, the committee recommends that this product should not be approved at this time, we would like the committee's sense of what further steps might be taken to make this a more acceptable product. For example, would further strengthening of the REMS allow for the reasonably safe use of this product, and if so, what changes would be needed?
- Would it be necessary to have additional data on the safety of using this product at the intervals permitted in proposed labeling, i.e., q 2 hours?
- Please comment on the proposed post-marketing observational study.
- Would comparative studies with currently approved IM products be needed to clearly demonstrate advantages for this product?
- We would also welcome discussion on any related topics that the committee feels are germane to this application.

cc:

HFD-130/TLaughren/MMathis/RLevin/FBecker/KUpdegraff

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/s/

THOMAS P LAUGHREN
11/14/2011

**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**

Label, Labeling, and Usability Study Review

Date: November 8, 2011

Reviewer: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Loxapine Inhalation Powder, 5 mg and 10 mg

Application Type/Number: NDA 022549

Applicant/sponsor: Alexza Pharmaceuticals

OSE RCM #: 2010-287

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

1 INTRODUCTION

This review evaluates the results of the Usability Studies for Adasuve and design of the device. Additionally, this review evaluates the device label as well as foil pouch, carton, prescribing information, and instructions for use labeling for Adasuve (Loxapine) Inhalation Powder for the potential to contribute to medication errors.

1.1 REGULATORY HISTORY

The original New Drug Application for Loxapine Inhalation Powder was submitted to the FDA on December 11, 2009. The proposed indication of use for this product is the rapid treatment of agitation associated with schizophrenia and bipolar disorder in adults. Loxapine Inhalation Powder is a subject of a 505(b)(2) application referencing Loxapine Tablets and Capsules (NDA 017525) and Loxapine Intramuscular Injection (NDA 018039) based on pharmacological, pharmacokinetic, toxicological, and clinical safety and efficacy profile.

The Application received a Complete Response on October 8, 2010, primarily due to safety issues related to pulmonary toxicity, particularly in patients whose pulmonary function may be compromised due to pulmonary-related disease states (i.e., COPD or asthma) or due to smoking. Additional issues identified in the Complete Response letter were drug product quality issues and lack of Human Factors Validation Study. Thus, a letter from the Center for Devices and Radiological Health (CDRH) requested the Applicant to conduct Human Factors Validation Study because the actuation of the device was associated with a loud clicking sound, prominent visible flash, and elevated inspired air temperature, all of which may startle an agitated patient and prevent the correct administration of the product. CDRH asked the Applicant to conduct the study with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting (See Appendix B for the Complete Response related to the Human Factors Study).

On November 19, 2010, the Applicant submitted the original protocol of the Human Factors Study. In the same submission, the Applicant stated that during the clinical studies the medication was administered via substantially similar device, Clinical Version 1 and 2, as the Commercial Version of the device (b) (4)

. The Applicant noted that no product complaints or comments related to noise, flash, or warm air were identified. The Applicant requested the FDA to provide comments to the Human Factors Validation Study protocol prior to End-of-Review meeting that took place on December 17, 2009. Specifically, the Applicant asked whether the Agency agrees with the design and methodology of the studies.

In the response to the submitted protocol, DMEPA and CDRH did not agree with the proposed protocol due flaws in design and methodology such as patient inclusion criteria, data gathering, data analysis, and post-analysis interview questions. DMEPA and CDRH recommended that the Applicant include patients with representative medical conditions (i.e., agitation due to schizophrenia or bipolar disorder) since these patients are the intended patient population. Additionally, DMEPA and CDRH recommended the

Applicant reverse the rating scale from 1=difficult and 7=easy to 1=easy and 7=difficult, adjusts orientation points for healthcare professionals and patients, include questions related to the location of the LED button for healthcare professionals and questions related to the clicking noise/flash of light/temperature change for patients in the post-test interview, and analyse the data based on user performance and subjective criteria. Furthermore, DMEPA and CDRH requested the Applicant include a discussion of whether assistance by the test administrators during the use of the product will be considered a task failure and the Applicant include specific test plan of how unexpected failures will be identified, recorded, and monitored.

During the meeting between the FDA and the Applicant on December 17, 2010, the Applicant agreed to modify the Human Factors Study to incorporate the majority of DMEPA's and CDRH's recommendations, except inclusion of the agitated patients. The Applicant proposed to include patients with bipolar disorder for schizophrenia who are not agitated. The FDA agreed that the studies should not include agitated patients (See Appendix C for the meeting minutes from December 17, 2010, related to Human Factors Study).

The Applicant submitted the revised protocol on February 4, 2011. DMEPA and CDRH provided recommendations regarding the revised protocol via email on March 18, 2011. In their response, CDRH and DMEPA recommended the Applicant include patients that had at least one episode of agitation requiring treatment in the intended environment of use and the Applicant explains why agitation with schizophrenia or bipolar disorder is not linked to hearing, or dexterity impairments. Additionally, they requested the Applicant provide clarification regarding the use environment of the product (i.e., ER, psychiatric clinic, etc.), user rating consistency, and definition/description of the task failure. Furthermore, CDRH and DMEPA requested the Applicant specify relevance of performance time (e.g., the entire task performed within 15 minutes) and how data will be collected in relation to task failure (See Appendix D to see the email from CDRH and DMEPA related to Human Factors Study).

On April 8, 2011, the Applicant submitted a third version of the protocol. DMEPA and CDRH agreed to this protocol via email on April 29, 2011.

The Applicant resubmitted the Application for Loxapine Inhalation Powder on August 4, 2011. In this submission, the Applicant submitted Summative Usability Test that tested the device and the instructions for use (IFU) and Supplemental Summative Usability Test that tested the changes in the device packaging and IFU after Summative Usability Test was performed.

The proposed proprietary name for this product, Adasuve, was found conditionally acceptable on May 6, 2010. However, since over a year has lapsed from the last time the proposed proprietary name was reviewed, DMEPA will re-review the proposed proprietary name, Adasuve, in a separate review once the request for the proprietary name review is submitted by the Applicant.

1.2 PRODUCT INFORMATION

Loxapine Inhalation Powder is indicated for the rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults. This product should be administered by

oral inhalation at the dose of 10 mg.

(b) (4)

Due to pulmonary toxicity risks such as bronchospams, especially to patients with compromised pulmonary function, the product should only be used in the healthcare settings that have pulmonary rescue treatments and appropriate medical personnel available. Because of such serious pulmonary risks, the product will have limited distribution REMS. The REMS is currently being discussed among multiple stakeholders.

Loxapine Inhalation Powder is supplied as the single-dose, single-use inhaler device. The device is packaged in a foil pouch and each carton contains five units of the product. After removing the inhaler from the foil pouch, the device is activated by pulling a plastic tab located at the opposite end of the mouthpiece. Tab removal illuminates the device's green LED light, which indicates that the device is ready to use. When the patient inhales through the mouthpiece, the movement of air inside the device initiates (via a breath sensor) a chemical reaction that very rapidly aerosolizes the drug that coats the internal heating plate. The aerosolized drug is then inhaled by the patient. While the drug is aerosolizing during inhalation process, a flash of white light, clicking sound, and temperature increase with the device occur. Once the drug is delivered, the green LED light automatically turns off, indicating that the medication has been delivered. However, the LED light automatically turns off after 15 minutes regardless whether the product has been inhaled or not.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Device Labels submitted on August 4, 2011 (See Appendix A)
- Foil Pouch Labeling submitted on August 4, 2011 (See Appendix A)
- Carton Labeling submitted on August 4, 2011 (See Appendix A)
- Insert Labeling submitted on August 4, 2011 (no image)

Additionally, two Human Factor studies, Summative Usability Test and Supplemental Summative Usability Test, were conducted to test the device and the Instructions for Use (IFU) labeling. The Summative Usability Test was conducted to test the Commercial Version of the device and the proposed IFU. The Supplemental Summative Usability Test was conducted to validate the changes made to the device packaging and the IFU after Summative Usability Test (See Appendix F for the Summary of the Studies).

We evaluated the results of the Usability Studies, the device design, and the IFU labeling based on our evaluation of the results of the Usability Studies, comments from the

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

participants, and the root cause analysis from the test administrators ((b) (4)).

3 RESULTS

The following section describes the findings of DMEPA’s evaluation of the Summative Usability Test and Supplemental Summative Usability Test, device design as well as device label, foil pouch, carton, IFU, and package insert labeling. Our evaluation of the device design and the IFU also considered the findings that were identified in Summative Usability Test and Supplemental Summative Usability Test.

3.1 HUMAN FACTORS USABILITY STUDIES

- The Applicant completed Summative Usability Test based on DMEPA’s and CDRH’s recommendations. The Applicant applied the same recommendations to the Supplemental Summative Usability Test.
- Tables 1, 2, and 3 describe the use failures detected in the usability studies. The Applicant interpreted the results of the studies to be acceptable because the Applicant considers (b) (4) are minor issues that carry minor safety impact. Thus, no additional modifications to the device or revisions to the IFU were implemented.
- The contributing factors to the errors were identified by the Applicant as the (b) (4)

Table 1: Summary of HCP use errors from Summative Usability Test.

Use error description	Number of participants	Number of occurrences	Total number of opportunities	Use error rate
(b) (4)				

Table 2: Summary of patient use errors in Summative Usability Test

Use error description	Number of participants	Number of occurrences	Number of opportunities	Use error rate
(b) (4)				

Table 3: Summary of HCP use errors from Supplemental Summative Usability Test

Use error description	Number of participants	Number of occurrences	Total number of opportunities	Use error rate
(b) (4)				

3.2 LABELS, LABELING, AND DEVICE ASSESSMENT

In addition to deficiencies identified in the Usability Studies, we identified the following areas of the device, label and labeling that are vulnerable to confusion that could lead to medication errors.

3.2.1 Product Design

- (b) (4)
-

3.2.2 Instructions for Use

- (b) (4)
-
-
-

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

3.2.3 Insert Labeling

- The dosage and administration instructions in the *Dosage and Administration* Section in Highlights of Administration and Full Prescribing Information are written in paragraph form instead of bullet points which make them difficult to read.
- The initial dose is not stated (e.g., 10 mg).

- [REDACTED] (b) (4)

3.2.4 Device Labels

- Dosage form and strength are not included on the label.
- Per 21CFR 201.10(i)(iv), the name of the manufacturer, packer, distributor is not included.
- Per 21 CFR 201.10(g)(1), brackets around the established name are not included.

3.2.5 Foil Pouch Labeling and carton Labeling

- The usual dosage statement and the route of administration are not included.
- The expiration date and lot number are more prominent than the most important information on the labeling such as proprietary and established names, dosage form, and strength.
- Proprietary and established names, dosage form and strength are not presented in usual manner and may be confusion.
- The established name and the NDC number appear twice and thus crowd the label.
- The “Single dose unit” statement is not followed by the statement “Discard after one use”.
- The “Rx Only” statement is prominent and completes with other important information.

4 DISCUSSION

The Applicant considers that potential harm related to [REDACTED] (b) (4) [REDACTED] are minor issues that carry minor safety impact. Thus, the Applicant interpreted the use failures that were made by the HCP and patients to be acceptable, because these use failures may result in dosing errors such as underdoses and dose omissions. As a result, no additional modifications to the device or revisions to the IFU were implemented. However, the dosing errors such as underdoses and dose omissions that can occur due to wrong usage technique can

potentially lead to sub-therapeutic levels of the medication, failure to relieve symptoms of agitation, prolong treatment times (e.g., patient has to be observed for a longer period of time or may be hospitalized), and exposure to additional doses of medication that carries significant safety risk of pulmonary toxicity. Thus, we do not agree with the Applicant's assessment of the safety risks related to the usability of the device to be minor. We suspect these failures occurred due to design of the device and the IFU. As a result, additional device modifications and IFU revisions should be implemented and re-tested in another Usability Study similar to the one already conducted with representative healthcare practitioners prior to the approval of the product.

All errors committed by the Healthcare Practitioners (HCP) and patients during Usability study may potentially result in underdoses or dose omissions. However, we noted that the most commonly occurring error was (b) (4)

[REDACTED]

[REDACTED] (b) (4)

This may lead to dosing errors such as underdoses or dose omissions, which may result in subtherapeutic levels of the medication, and inability to relieve the symptoms of agitation. Sub therapeutic doses may result in the need for additional doses of this medication.

[REDACTED] (b) (4)

Thus, IFU should include a statement regarding the fact that it is normal for the patient to see a flash of light, hear a clicking sound, or feel that the device gets warmer during inhalation process.

5 CONCLUSIONS AND RECOMMENDATIONS

The studies were performed according to the protocol recommendations that were provided by CDRH and DMEPA. However, the Usability studies have not demonstrated the device and the IFU are sufficient to ensure patients can administer this product safely.

Our evaluation of the device design and IFU labeling identified areas of improvement based on the Usability Tests that will help minimize the risk of medication errors associated with the use of the product.

Furthermore, our evaluation of the device label, foil pouch, carton, and prescriber information labeling also identified areas that introduce vulnerability that can lead to medication errors.

Thus, Section 5.1, Comments to the Division contains our recommendations regarding design of the device, IFU, and prescriber information labeling. Section 5.2, Comments to the Applicant contains our recommendation regarding device labels, foil pouch, and carton labeling. These recommendations should be implemented and re-tested through Usability studies similar to the ones completed prior to the marketing of the product.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Sandra Griffith at 301-796-2445.

5.1 COMMENTS TO THE DIVISION

A. Usability Studies

We recommend re-testing the device and the IFU through the Usability Study after additional device modifications listed in section B and IFU revisions listed in section D to ensure the safety of the device. We disagree with the Applicant's assessment that potential harm related to (b) (4)

are minor issues that carry minor safety impact. The dosing errors such as underdoses and dose omissions that can occur due to wrong usage technique can potentially lead to sub-therapeutic levels of the medication, failure to relieve symptoms of agitation, prolong treatment times (e.g., patient has to be observed for a longer period of time or may be hospitalized), and exposure to additional doses of medication that carries significant safety risk of pulmonary toxicity.

B. Product Design

1. We recommend relocating the product's label containing the proprietary and established name, dosage form, and strength to the side where the LED button located. We recommend this design change to help minimize wrong technique errors in which participants do not verify whether LED light is illuminated or that the light turned off indicating that the device has been activated or the dose has been delivered respectively. (b) (4)

2. We recommend addition of the label or embossment next to LED light stating what it means when LED light is lit and when it is turned off (e.g., "on=ready to

use” or “off=device actuated). We recommend this design change to signify the meaning of this feedback mechanism and to help minimize wrong technique errors in which participants do not verify whether LED light is illuminated or that the light turned off indicating that the device has been activated or the dose has been delivered respectively.

3. We recommend orienting the device in a pouch in such a manner, that the LED light and the relocated label containing the proprietary and established names, dosage form, and strength are facing the same side as the IFU on the foil labeling. We recommend this change to ensure easy identification of the label and the LED light on the device as well as to help eliminate wrong technique errors in which participants do not verify whether LED light is illuminated or turned off.

(b) (4)

C. Prescriber Information Labeling

1. *Dosage and Administration* Section, Highlights of Prescribing Information

a.

(b) (4)

- b. Revise the first bullet point “

(b) (4)

as follows:

- *The starting dose is 10 mg by oral inhalation.*

(b) (4)

We recommend this revision to help clarify the dosage and administration information. As presented, the information is unclear, cumbersome, and confusing.

2. Section 2, *Dosage and Administration*, Full Prescribing Information

a.

(b) (4)

- b. We recommend revising the entire Section as follows:

The recommended initial dose of ADASUVE is 10 mg administered by oral inhalation.

(b)
(4)

Adasuve is a single-dose, single-use disposable inhaler. Discard each inhaler after one use.

We recommend this revision because pieces of important, relevant information are scattered throughout the section in an unclear, and confusing

way. (b) (4)

- c. Please add sub-Section 2.1, Administration to Section 2. Since healthcare professionals are going to be assisting patients to administer this drug, administration instructions should be available in the prescribing information in addition to separate IFU placed with the device inside the foil pouch.
3. Section 3, *Dosage Forms and Strengths*, Full Prescribing Information

We recommend revising the description in this section as follows:

Adasuve is a single-dose, single-use disposable inhaler containing 10 mg of loxapine base. (b) (4)

We recommend this revision to emphasize that the product is an inhaler containing a single dose of the medication and should be used only once.

4. Section 16.1, *How Supplied*, Full Prescribing Information

We recommend revising this section to emphasize that the product is an inhaler containing a single dose of the medication that should be used only once as well as to clarify how Adasuve is supplied. Thus, please revise this section as follows:

(b) (4)


ADASUVE 10 mg (NDC 51097-002-01) is a single-dose, single-use, disposable inhaler containing 10 mg of loxapine, provided in a sealed foil pouch. ADASUVE, 10 mg is supplied in a carton of 5 units per carton.




See Appendix A for the proposed prescriber information labeling changed by DMEPA.

D. Instructions For Use (IFU) Labeling

1. Please revise the word (b) (4) to state “inhaler” throughout the IFU. The word (b) (4) is imprecise and could be confusing to healthcare practitioners or patients.
2. Step 2: Please add a sentence that reads “Discard the inhaler after one use” after the sentence “Use within 15 minutes after removing the tab to prevent automatic deactivation of the product.” We recommend this revision to ensure that healthcare providers dispose of the device after patient uses it once. (b) (4)
3. Step 4: Inhale
 - a. Please include the information regarding the fact that it is normal for the patient to see a flash of light, hear a clicking sound, or feel that the inhaler gets warmer while inhaling from the inhaler after the first sentence “Inhale through mouthpiece with a steady deep breath”. We recommend this revision

to help ensure patients inhale the medication correctly without being interrupted, startled, or frightened by flash of light, noise, or hotter temperature of the device. (b) (4)



- b. Step 4: Please add a second sentence in the box stating “The green light will automatically turn off after the medication has been delivered.” We recommend the addition of this sentence to help patients and practitioners identify that a dose has been delivered.
4. Step 5: Hold Breath
 - a. Please revise the image, so that a person in the picture has puffy cheeks and pressed lips to imitate a person holding their breath. The graphic does not depict the instruction very well. (b) (4)
 - b. Please specify how long a patient should hold their breath (e.g., remove the mouthpiece from the mouth and hold breath for 5 seconds). (b) (4)
5. In the ‘NOTE’ section, please specify how many times a patient can repeat steps 3 through 5. (b) (4)
6. Please provide further instructions regarding the steps that should be taken if the LED light does not turn off after Steps 3 through 5 were performed by a patient a specified number of times. We recommend addition of this important information because it is unclear what the healthcare providers should do in the event of the device malfunction or dosing errors such as underdose or dose omission occur.

5.2 COMMENTS TO THE APPLICANT

A. Device Label

1. Include the dosage form immediately following the established name, followed by the strength [i.e. (loxapine) inhalation powder, 10 mg]. The proprietary and established names, dosage form, and strength should be relocated to the side of

the device that has the LED light. The lot number, expiration date, NDC, and PNL numbers can remain on the opposite side.

2. Per 21 CFR 201.10(g)(1), include brackets around the established name so that the relationship between the proprietary name and established name is clear.
3. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
4. Per 21 CFR 201.10(i)(iv), include the name of the manufacturer, packer, or distributor on the opposite side of the LED light.
5. Per 201.100 (b)(2) include the route of administration if space permits.

B. Foil Pouch Labeling (Front Side)

1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and has the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Per 21 CFR 201.100(b)(2) or 201.55, include the usual dosage statement, if space permits.
3. Per 21 CFR 201.100(b)(3), include the route of administration, if space permits.
4. Increase the prominence of the proprietary and established names as they should be the most prominent information on the label. Currently, they can be overlooked by other information on the label.
5. Present the proprietary name followed by the established name immediately followed by the dosage form then the strength. Present in the following manner:

Adasuve
(loxapine) inhalation powder
xx mg

6. Remove “loxapine” following the strength as the established name is already included following the proprietary name and as it crowds the label.
7. Include a space between the number and the unit in the presentation of the strength (i.e. 5 mg rather than 5mg).
8. Include the statement “Discard after one use” following the single dose unit statement.
9. Delete one of the NDC numbers as there are two of them printed on the principle display panel.
10. Decrease the prominence of the lot number and expiration date as this information completes with the most important information on the label such as the proprietary and established name, dosage form, and strength.

11. Decrease the prominence of the “Rx Only” statement by relocating it to a less prominent position of the label.
12. Consider additional differentiation between 5 mg and 10 mg strength of the Adasuve through additional use of color, boxing, or some other means. Presently, labeling for both strengths appear similar to each other for the exception of the colored strengths, which can lead to selection of the wrong strength.

C. Foil Pouch Labeling (Back Side)

1. Revise the word (b) (4) to state “inhaler” throughout the abbreviated IFU on the pouch labeling. The word (b) (4) is imprecise and could be confusing to healthcare practitioners or patients.

2. Step 4: Inhale

- a. If space permits, add the sentence “It is normal to see a flash of light, hear a clicking sound, or feel that the inhaler gets warmer as you inhale.” after the first sentence “Inhale through mouthpiece with a steady deep breath”. We recommend this revision to help ensure patients inhale the medication correctly without being interrupted, startled, or frightened by flash of light, noise, or hotter temperature of the device. Twenty four of the 32 patient participants in the Summative Usability Study reported noting the device emitting flash or light and or sound. (b) (4)

- b. In the box, add a sentence “Check the green light” prior to the sentence “The green light turns off after the medication is delivered”. (b) (4)

3. Please specify how long a patient should hold their breath (e.g., remove the mouthpiece from the mouth and hold breath for 5 seconds). (b) (4)

D. Carton Labeling

1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and has the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

2. Increase the prominence of the proprietary and established names as they should be the most prominent information on the label. Currently, they can be overlooked by other information on the label.

3. Present the proprietary name followed by the established name immediately followed by the dosage form then the strength. Present in the following manner:

Adasuve
(loxapine) inhalation powder
xx mg

4. Increase the prominence of the route of administration by using bigger font type or bolding as this important information may be overlooked because it appears in the same font size as other information on the label such as storage temperature
5. Remove “loxapine” following the strength as the established name is already included following the proprietary name and as it crowds the label.
6. Include a space between the number and the unit in the presentation of the strength (i.e. 5 mg rather than 5mg).
7. Include the statement “Discard after one use” following the single dose unit statement.
8. Delete one of the NDC numbers as there are two of them printed on the principle display panel.
9. Decrease the prominence of the lot number and expiration date as this information completes with the most important information on the label such as proprietary and established name, dosage form, and strength.
10. Decrease the “Rx Only” statement by decreasing the font size as this statement completes with the most important information on the label such as proprietary and established name, dosage form, and strength.
11. Consider additional differentiation between 5 mg and 10 mg strength of the Adasuve through additional use of color, boxing, or some other means. Presently, labeling for both strengths appear similar to each other for the exception of the colored strengths, which can lead to selection of the wrong strength

4 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)
immediately following this page

Appendix B: Complete Response from October 8, 2010 Regarding Human Factors Studies.

Center for Devices and Radiological Health (CDRH)

1. Based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, a prominent visible flash, and elevated inspired air temperature. These phenomena caused a startle response in some cases, which resulted in incomplete inhalation. Under these conditions, patients unfamiliar with the device may discontinue inhalation and, therefore, not receive the full, intended dose. In fact, it is not clear that the clinical studies (301 and 302) were conducted in patients substantially similar to those for whom this drug might be most useful in the community. It is our impression that the most likely patients to be considered for this product would be patients in an emergency setting in which health care providers may not be familiar with the patients' histories and the patients would not be familiar with this product. Thus, we request that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting.

You must address the following:

- a. A human factors validation report that includes:
 - i. A detailed analysis of use performance and subjective data;
 - ii. Evaluation and documentation of user performance, use errors and task failures
 - iii. An evaluation of the effectiveness of proposed mitigation strategies (training, device labeling, etc.) through simulated use scenarios;
 - iv. Discussion of how unanticipated failures can be handled; and
 - v. Discussion of any further mitigation strategies necessary and if further validation is necessary.
- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to safe use of the product. The study must evaluate feedback provided by test participants, which focuses on their ability to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
- c. You must conduct a thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients. This analysis should include the independent and integrated aspects of both the device and user interactions. The risk analysis should address whether the device is used in ways that were not anticipated, especially if the device use environment affects device utility and user comprehension. This risk analysis should also include a discussion of the mitigations against use-related risks, and it should evaluate the effectiveness of the mitigations, based on the human factors validation study results.

Appendix C: Meeting Minutes from December 17, 2010 Related to the Human Factors Studies Protocol.

Human Factors Assessment

Question 7: Does the Agency agree that the design and methodology for the proposed human factors validation study is adequate to validate that the product can be used effectively in the proposed clinical setting? In particular, does the Agency agree that the directed task scenarios, the evaluation methodologies, and the enrollment criteria for representative healthcare providers and representative patients are adequate for this study?

***Preliminary Comments:** We do not agree. Refer to the following detailed comments on the proposed human factors validation study design and methodology. Please note that comments provided to specific sections of the protocol may require revisions to other sections of the protocol.*

However, please see the following comments from CDRH and DMEPA:



Discussion at Meeting: *Alexza agreed to modify the human factors study as per recommendations #2 through #10. To address comment #1, Alexza proposed to include patients with bipolar disorder or schizophrenia who are not agitated. We agreed that the studies should not include agitated patients. We requested that the sponsor revise and formally submit the protocol for review and comments.*

Appendix D: CDRH and DMEPA Email from March 18, 2011 to the Applicant regarding Human Factors Study Protocol

Dear Christine,

Please refer to your New Drug Application (NDA 022549) for Adasuve (loxapine) Inhalation Powder and your submission dated February 4, 2011, received February 7, 2011, containing a revised protocol for the human factors validation study.

The Center for Devices and Radiological Health (CDRH) along with the Division of Medication Error Prevention and Analysis (DMEPA) have reviewed your submission and have the following comments/recommendations:

(b) (4)



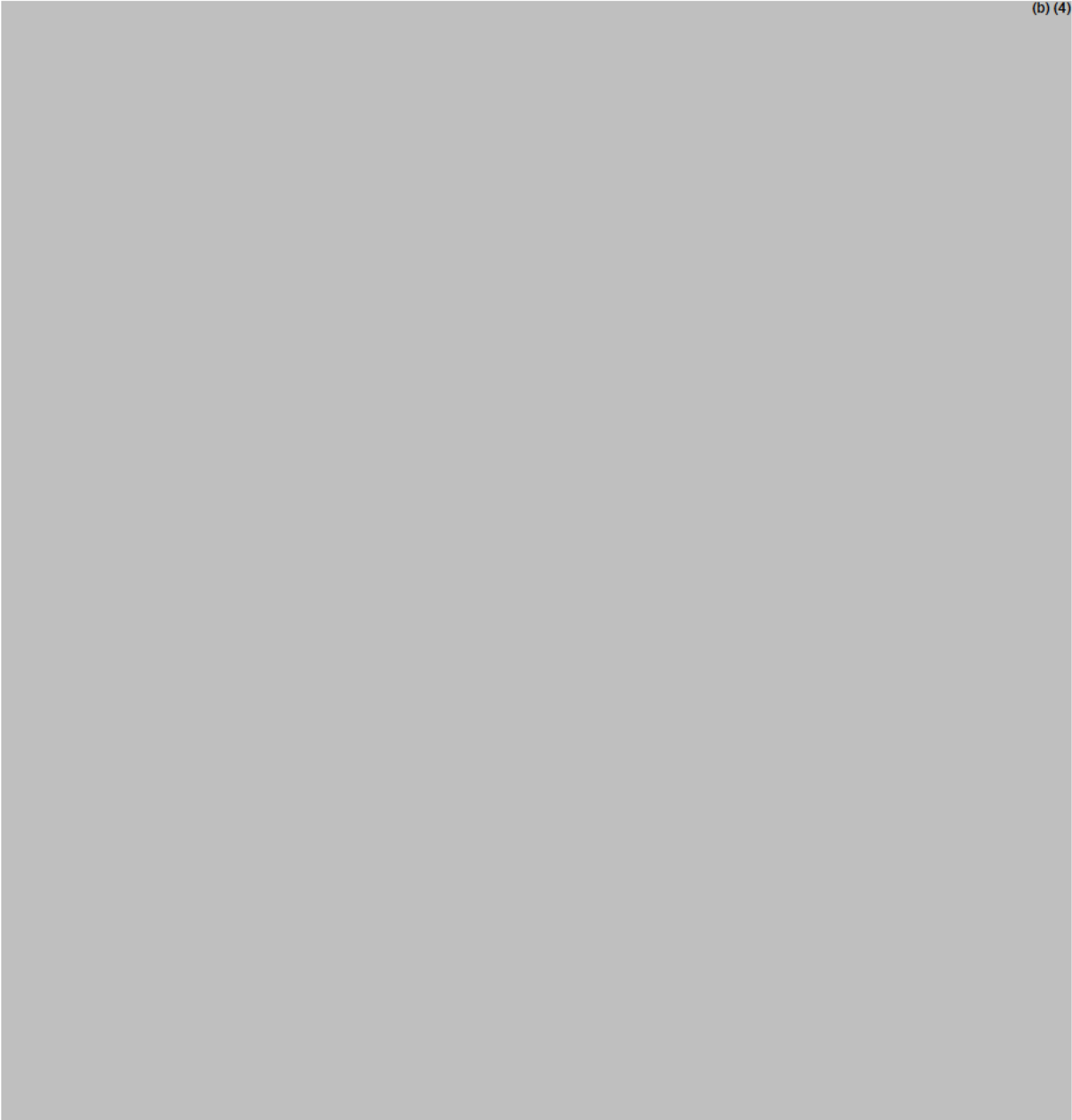
Please let me know if you have any questions.

Best regards,

Kim

Kimberly Updegraff, RPh, MS, RAC
Senior Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201
Email: Kimberly.Updegraff@fda.hhs.gov

Appendix E: The IFU used in the Clinical Studies (004-301 and 004-302) submitted to the FDA via email on October 19, 2011



Appendix F: Summary of the Summative Usability Test and Supplemental Summative Usability Test

The Summative Usability Test was conducted as follows:

Healthcare practitioners:

- 15 Healthcare professionals (8 nurses and 7 physicians). The healthcare professionals work in psychiatric environment (e.g., hospitals in-units, outpatient clinics, private practice) and emergency departments.
- Healthcare practitioners interacted with “actor” patients that pretend to be agitated to provide consistent patient interaction.
- Test environment included noise similar to the healthcare setting noise: played soundtrack of footsteps, conversations, cabinets opening and closing, rolling carts, beeps of medical devices, telephone ringing.
- One healthcare practitioner task was considered to prepare the device for use while using IFU and direct the “actor” patient to use the device.
- The healthcare practitioners had to perform this task 10 times in randomized order. Two times the healthcare practitioner had to perform task under “normal” conditions (i.e., no product quality issues or distractions) and 8 times healthcare practitioner had to perform a task when the device was purposefully adjusted to malfunction (i.e., pulled tab, LED light not turning on or off) or distractions were used (i.e., “actor” patient asked questions, or pretended to want to go home, phone rang, patient exhaled into the device instead of inhaling).
- After the test was administered, the test administrators asked the health care practitioners open-ended and closed-ended questions regarding the use of the device and the steps that healthcare practitioners might have failed. Based on the responses and through observations, root causes were identified by the test administrators.

Patients

- 32 non-agitated patients (15 patients with schizophrenia and 15 patients with bipolar disorder) that has received one or more treatment for agitation in the past with various education levels.
- Patients interact with “actor” healthcare practitioners to provide consistent healthcare practitioner interaction.
- Test environment included noise similar to the healthcare setting noise: played soundtrack of footsteps, conversations, cabinets opening and closing, rolling carts, beeps of medical devices, telephone ringing.
- One patient task was considered to follow the “actor” healthcare practitioner instructions to use the device.
- Patients had to perform this task 5 times in randomized order. Three times the patient had to perform the task under “normal” conditions (no distractions or product quality issues) and two times patient had to perform the task while

distractions were used (i.e., phone rang or healthcare practitioner asked a question when the patient is about to inhale).

- After the test was administered, test administrators asked the patients open-ended and closed-ended questions regarding the use of the device and steps the patients might have failed. Based on the responses and through observations, root causes were identified by the test administrators.

Supplemental Summative Usability Test

- Only healthcare practitioners were enrolled.
- 15 Healthcare professionals (8 nurses and 7 physicians). The healthcare professionals work in psychiatric environment (e.g., hospitals in-units, outpatient clinics, private practice) and emergency departments.
- Healthcare practitioners interacted with “actor” patients that pretend to be agitated to provide consistent patient interactions.
- Test environment included noise similar to the healthcare setting noise: played soundtrack of footsteps, conversations, cabinets opening and closing, rolling carts, beeps of medical devices, telephone ringing.
- One healthcare practitioner task was considered to prepare the device for use while using IFU and direct the “actor” patient to use the device.
- The healthcare practitioners had to perform this task 6 times in randomized order. Three times the healthcare practitioner had to perform task under “normal” conditions (i.e., no product quality issues or distractions) and three times healthcare practitioner had to perform a task when the device was purposefully adjusted to malfunction (i.e., LED light not turning on or off) or distractions were used (i.e., “actor” patient exhaled into the device instead of inhaling).
- After the test was administered, the test administrators asked the health care practitioners open-ended and closed-ended questions regarding the use of the device and the steps that healthcare practitioners might have failed. Based on the responses and through observations, root causes were identified by the test administrators.

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/s/

YELENA L MASLOV
11/08/2011

ZACHARY A OLESZCZUK
11/10/2011

CAROL A HOLQUIST
11/10/2011



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Ave
Silver Spring, MD 20993

NDA 022549**Response to Consult Request**

Date: November 4, 2011
From: Nayan Patel, Biomedical Engineer, Anesthesiology and Respiratory Device Branch, Division of Anesthesiology (ARDB), General Hospital, Infection Control, and Dental (DAGID), CDRH
Through: Sugato De, M.S. Combination Products Team Lead, DAGID/ODE/CDRH
Lex Schultheis, M.D., Ph.D, ARDB Chief, DAGID/ODE/CDRH
Kwame Ulmer, M.S. Deputy Division Director, Science and Policy, DAGID/ODE/CDRH
To: David Claffey, Ph.D, Division of Psychiatry Products, CDER
Kimberly Undegraff, RPh, MS, RAC, Senior Regulatory Project Manager
Thomas Laughren, M.D., Division Director, Division of Psychiatry Products, CDER
Re: NDA 022549 Alexza Staccato Loxapine for Treatment of Agitation

I. Summary

We have reviewed the information pertaining to the device component of this submission.

The sponsor has adequately addressed the remaining two device/engineering related issues (characterizing total mass of drug delivered to lungs and worst case evaluation of heat package failure). At this time, there are no more device/engineering related issues.

Please request the sponsor provide additional information for the Human Factors concerns outlined in the recommendation section of Lt. Nguyen's memo.

II. Purpose of Consult

The Division of Psychiatry Products (CDER) has requested a consult from CDRH regarding the review of an NDA submission, # 022,549, Staccato Loxapine manufactured by Alexza Pharmaceuticals, Inc. This is a re-submission based on the Agency's Complete Response letter issued 10/6/2011. The CR letter consisted of a request for a human factors validation study along with two other requests for device performance testing.

For this resubmission, I am the device lead reviewer and I have consulted Lt. QuynhNhu Nguyen to evaluate the Human Factors information provided in the submission. This review will focus on the sponsor's response to additional device performance testing. For a review of the Human Factors information, please see Lt. Nguyen's review memo.

III. Device Description

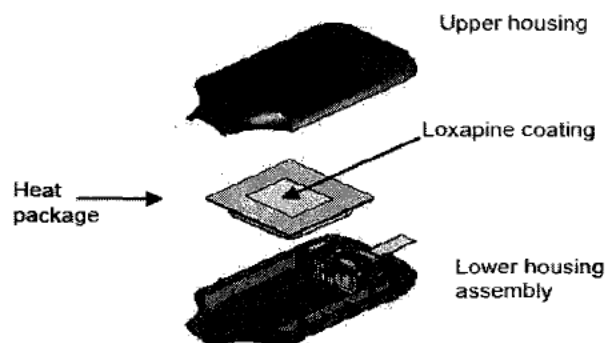
Staccato® Loxapine for Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg.

Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza. Oral

inhalation through the 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 rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

Staccato Loxapine (5 mg and 10 mg) has been developed 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.

Figure 1. Schematic of Staccato Loxapine



Note: Pouch not shown in schematic. (b) (4) are processing aids that are evaporated during drug product manufacturing.

IV. Intended Use

The proposed combination product is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder.

V. Discussion

Presented below (*in italics*) are the questions as presented to the sponsor followed by CDRH response in formal font.

1. Please see the consult memo from Lt. Nguyen.
2. *Pulmonary safety studies revealed clinically significant reductions in FEV1 in subjects with asthma or COPD, as well as in healthy subjects. The site of deposition of inhaled particles and the intrapulmonary dose fraction may be related to the observed reduction in FEV1. Although this would be a challenging issue to resolve, we ask that you consider approaches to better understand the etiology of airway reactivity associated with loxapine inhalation powder. In particular, you should propose approaches to characterizing the total mass of drug and ignition products that are deposited in the lung.*

Response Adequate

At the End of Review meeting, agreement was reached with the sponsor that no additional studies were necessary. Per our request, data collected during the development program on aerosol particle size distribution has been presented for each individual cascade impaction run.

Effect of Varying Airflow Rates on Aerosol Properties

The sponsor evaluated the effect of varying airflow rates on aerosol properties at 15 (50% of nominal), 30 (nominal) and 45 LPM (150% of nominal). Development testing has shown that Staccato Loxapine's aerosol performance is robust at 15 and 45 LPM for both 5 and 10 mg doses. Although no pre-defined acceptance criteria were applied to the test results at 15 and 45 LPM, the results are consistent with the criteria applied to the other product characterization studies. The emitted dose (Table 1) was $\geq 75\%$ of the mean coated dose at all flow rates tested.

The aerosol particle size is established as the drug vapor cools and condenses into particles, which subsequently collide and aggregate to the final particle size. The extent of aggregation is affected by the amount of airflow diluting the particles, which is a function of the inhalation flow rate. However the MMAD (Table 1) fell within the range of desired particle sizes for deep lung deposition of drug (1.0 to 3.5 μm) over the full range of flow rates tested. Individual MMAD values were 1.4 to 2.6 μm for the 5 mg dose and 1.6 to 3.0 μm for the 10 mg dose. There were no individual impurities greater than 0.1% detected for either dose over the full range of flow rates.

Table 1. Effect of Airflow (Inhalation) Rate on Aerosol Performance

Flow Rate (LPM)	Mean Emitted Dose, % CD ¹		MMAD, μm (GSD) ¹	
	5 mg	10 mg	5 mg	10 mg
15	87 \pm 5	94 \pm 2	2.4 \pm 0.1 (2.1 \pm 0.0)	2.8 \pm 0.1 (2.4 \pm 0.1)
28.3 / 30 ²	92 \pm 3	96 \pm 3	1.8 \pm 0.1 (2.0 \pm 0.0)	2.1 \pm 0.1 (2.2 \pm 0.1)
45	91 \pm 3	100 \pm 1	1.5 \pm 0.1 (2.1 \pm 0.0)	1.7 \pm 0.0 (2.1 \pm 0.0)

¹ n = 3 per airflow/lot with 3 drug product lots tested per dose, giving n = 9 total for each airflow/dose combination

² 28.3 LPM for emitted dose and aerosol impurities; 30 LPM for particle size distribution

To investigate regional deposition, the mouth-throat model airway developed by Finlay et al. (Stapleton, 2000) was used. This is an idealized mouth-throat geometry, which was developed based on literature, CT scans of patients, and observations of living subjects. The model consists of four pieces (shown in Figure 2), which are intended to represent the (1) anterior mouth, (2) posterior mouth, (3) pharynx, and (4) trachea. The trachea piece is connected to a filter, which is connected to a vacuum source, which pulls air through the model. With this setup, it is presumed that drug that does not deposit in the mouth-throat (i.e., the portion of the drug in the filter) would deposit in the bronchial and/or alveolar regions of the respiratory system.

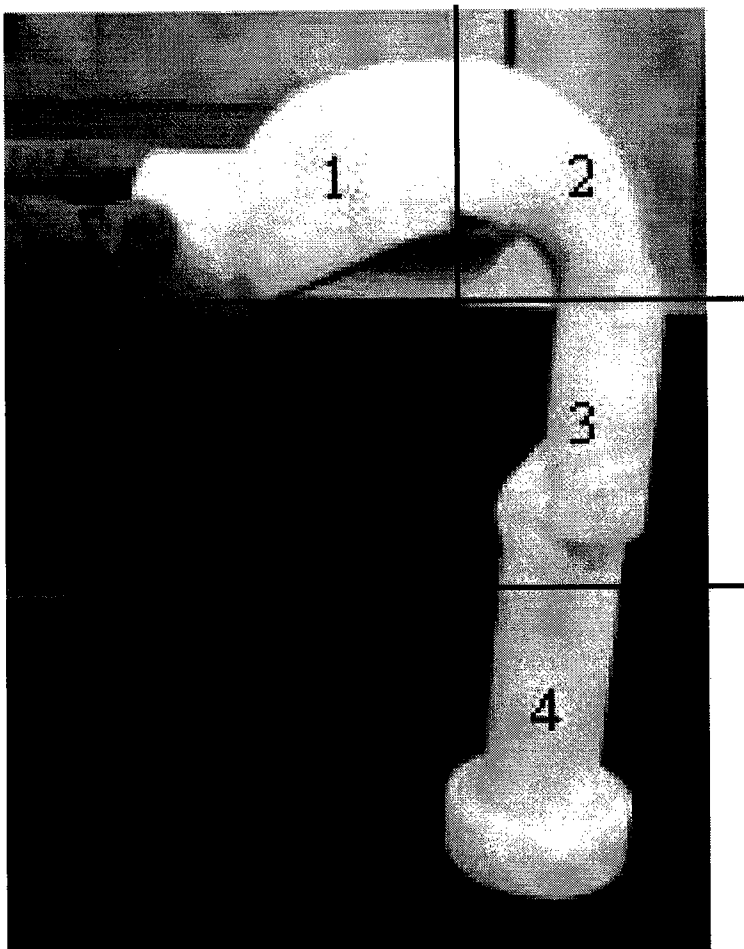


Figure 2. Photograph of Mouth-through Model Airway

Over the full range of flow rates, at least 88% of the emitted dose is deposited in the filter (corresponding to the bronchial + alveolar regions), as shown in Table 2. The portion of the coated dose left unvaporized on the heat package decreases slightly with flow rate, resulting in a slight increase in the overall emitted dose with flow rate, which is consistent with Table 1.

Table 2. Deposition in Mouth-Throat Model Airway and Filter over Range of Airflow Rates

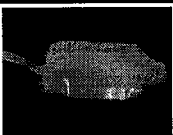
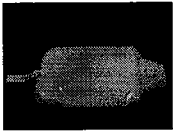



Flow Rate (LPM)	Average Deposition (% ED)	
	Mouth-throat	Bronchial and alveolar regions (Filter)
15	11.6 ± 1.4	88.4 ± 1.4
28.3	11.3 ± 1.1	88.7 ± 1.1
45	10.6 ± 1.5	89.4 ± 1.5
60	11.5 ± 0.6	88.5 ± 0.6
80	9.0 ± 0.9	91.0 ± 0.9

Effect of Device Orientation on Aerosol Properties

The sponsor tested the device in five orientations which represents the range of possible use orientations. The aerosol properties (emitted dose, aerosol impurities, and aerosol particle size distribution) were measured at each orientation.

As shown in Table 3, aerosol at all five device orientations met the pre-defined acceptance criteria for emitted dose and particle size distribution, indicating robustness of Staccato Loxapine for all of the potential use orientations tested. In addition, no aerosol impurities greater than 0.1% were observed for any of the orientations.

Table 3. Effect of Use Orientation on Aerosol Performance

Device Orientation		Property (Acceptance Criteria)			
		Mean Emitted Dose, % CD ($\geq 75\%$ CD)		MMAD, μm (GSD) (MMAD = 1.0-3.5 μm , GSD ≤ 2.5)	
		5 mg	10 mg	5 mg	10 mg
Alexza logo facing up (nominal) ¹		92 \pm 4	93 \pm 1	1.7 \pm 0.0 (2.0 \pm 0.0)	2.1 \pm 0.1 (2.2 \pm 0.0)
Alexza logo facing down ²		92 \pm 2	95 \pm 3	1.9 \pm 0.1 (2.0 \pm 0.0)	2.1 \pm 0.1 (2.2 \pm 0.0)
Sideways (rotated 90 degrees from nominal) ²		90 \pm 5	94 \pm 2	1.9 \pm 0.1 (2.0 \pm 0.0)	2.0 \pm 0.1 (2.2 \pm 0.1)
Vertical with the mouthpiece facing up ³		88 \pm 2	93 \pm 3	2.0 \pm 0.2 (2.0 \pm 0.1)	2.1 \pm 0.1 (2.3 \pm 0.1)
Vertical with the mouthpiece facing down ²		90 \pm 3	89 \pm 4	1.8 \pm 0.0 (2.0 \pm 0.0)	2.0 \pm 0.1 (2.2 \pm 0.3)

¹ n = 3 (per lot) for emitted dose, n = 6 (per lot) for 5 mg particle size distribution, and n = 3 (per lot) for 10 mg

particle size distribution

² n = 3 (per lot) for emitted dose, n = 3 (per lot) for particle size distribution

³ n = 3 (per lot) for emitted dose, n = 9 (per lot) for 5 mg particle size distribution, and n = 3 (per lot) for 10 mg particle size distribution

Effect of Altitude on Aerosol Properties

Because the heat package expands during the operation of Staccato Loxapine, the drug product was tested at simulated altitude to evaluate if the reduced pressure environment resulted in any changes to the aerosol properties. The Staccato Loxapine aerosol properties (emitted dose, aerosol impurities, and aerosol particle size distribution) were evaluated following actuation in a reduced pressure environment (564 mm Hg) simulating ~8000 ft altitude (Federal Aviation Regulation 25). As shown in Table 4, all test results met the predefined acceptance criteria for emitted dose and particle size distribution, indicating robustness of Staccato Loxapine when tested at ~8000 ft altitude. No aerosol impurities greater than 0.1% were detected.

Table 4. Effect of Altitude on Aerosol Performance

Environmental Pressure (mm Hg)	Property (Acceptance Criteria)			
	Mean Emitted Dose ¹ , % CD (≥75% CD)		MMAD ¹ , μm (GSD) (MMAD = 1.0-3.5 μm, GSD ≤2.5)	
	5 mg	10 mg	5 mg	10 mg
~760 ² (nominal/sea level)	92 ± 3	97 ± 2	1.8 ± 0.1 (2.0 ± 0.0)	2.0 ± 0.1 (2.1 ± 0.1)
564 (~8000 ft altitude)	91 ± 4	91 ± 2	2.0 ± 0.1 (2.2 ± 0.1)	2.4 ± 0.1 (2.3 ± 0.1)

¹ n = 3 per lot with two lots tested per dose, for n = 6 total for each altitude/dose

² Ambient laboratory conditions

Effect of Humidity on Aerosol Properties

The Staccato Loxapine aerosol properties (emitted dose, aerosol impurities, and aerosol particle size distribution) were evaluated in environments having relative humidity (RH) in the range of 15% to 90%. As shown in Table 5, all test results met the pre-defined acceptance criteria. No aerosol impurities greater than 0.1% were detected.

Table 5. Effect of Humidity on Aerosol Performance

Relative Humidity, %RH (Ambient Temp. = 25 ± 2°C)	Property (Acceptance Criteria)			
	Mean Emitted Dose ¹ , % CD (≥75% CD)		MMAD ¹ , μm (GSD) (MMAD = 1.0-3.5 μm, GSD ≤2.5)	
	5 mg	10 mg	5 mg	10 mg
15 ± 5	91 ± 1	94 ± 1	1.8 ± 0.1 (2.0 ± 0.0)	2.2 ± 0.0 (2.2 ± 0.1)
50 ± 5	88 ± 2	92 ± 1	1.9 ± 0.2 (2.0 ± 0.0)	2.2 ± 0.1 (2.2 ± 0.0)
90 ± 5	87 ± 4	93 ± 2	1.9 ± 0.0 (2.0 ± 0.0)	2.2 ± 0.2 (2.1 ± 0.1)

¹ n = 3 per lot with two lots tested per dose, for n = 6 total for each humidity/dose

Effect of Ambient Temperature on Aerosol Properties

The Staccato Loxapine aerosol properties (emitted dose, aerosol impurities, and aerosol particle size distribution) were evaluated in environments having ambient temperature in the range of 15°C to 30°C. As shown in Table 6, all test results met the pre-defined acceptance criteria. No aerosol impurities greater than 0.1% were detected.

Table 6. Effect of Ambient Temperature on Aerosol Performance

Ambient Air Temperature, °C (Relative Humidity = 50%±5%)	Property (Acceptance Criteria)			
	Mean Emitted Dose ¹ , % CD (≥75% CD)		MMAD ¹ , µm (GSD) (MMAD = 1.0-3.5 µm, GSD ≤2.5)	
	5 mg	10 mg	5 mg	10 mg
15 ± 2	90 ± 2	95 ± 3	1.8 ± 0.1 (2.0 ± 0.0)	2.0 ± 0.1 (2.2 ± 0.0)
Ambient laboratory conditions	92 ± 3	97 ± 2	1.8 ± 0.1 (2.0 ± 0.0)	2.0 ± 0.1 (2.1 ± 0.1)
30 ± 2	93 ± 2	96 ± 2	1.9 ± 0.0 (2.0 ± 0.0)	2.1 ± 0.0 (2.1 ± 0.0)

3. The worst case simulation test that was conducted during product development consisted of 1 mm holes that were drilled in specific areas of the heat package. However, we request that you conduct a more realistic and meaningful worst case simulation, such as failure of (b) (4) along a seam that holds the tray and the lid together. This type of scenario is expected to more realistically simulate a possible manufacturing defect. The purpose of the heat package worst case simulation to evaluate catastrophic heat package failure was to anticipate potential injury to a patient when making a risk benefit determination for the product. To understand the potential clinical risk, you must conduct a more realistic worst case testing while measuring temperature inside an anatomical model of the upper airway during simulated inspiration.

Response Adequate

Following discussions with CDRH, Alexza conducted a worst case evaluation of a heat package failure (b) (4). At the End of Review meeting, the Agency acknowledged that this new information was sufficient to address this concern, and that this information be formally submitted.

Heat packages with missing (b) (4) were assembled into devices, which were tested for aerosol temperature. Five types of compromised heat packages were tested, along with uncompromised heat packages as a control group.

The sponsor used their standard protocol for measuring aerosol temperatures. This method consists of collecting temperature measurements from an array of seven thermocouples placed just outside the exit plane of the device mouthpiece. The maximum air temperature on each thermocouple is recorded, and the average of the seven maxima is subsequently converted to wet bulb temperature using standard psychrometric equations. Measuring air temperature very close to the mouthpiece, and at maximal proximity to the heat package, results in the highest possible temperature value and represents the most conservative approach to evaluating safety.

Figure 3 and Table 7 show the results of this study.

Figure 3. Aerosol Temperature from Devices with Compromised Heat Packages
N=3 per condition. Data points represent mean \pm one standard deviation.

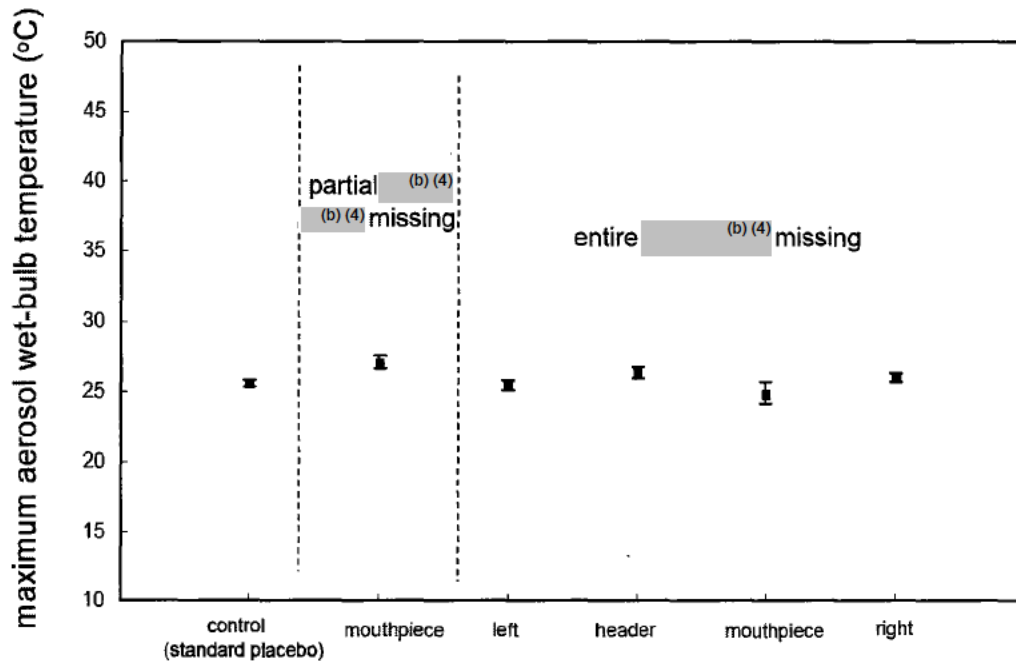


Table 7. Aerosol Temperature from Compromised Heat Packages


Heat Package Condition	Avg. Maximum Aerosol Wet Bulb Temperature \pm 1 Std. Dev. (°C) (n=3)
Control (standard placebo)	25.5 \pm 0.2
(b) (4) partially missing on the mouthpiece side	27.1 \pm 0.4
entirely missing on the left side	25.4 \pm 0.4
entirely missing on the header side	26.4 \pm 0.4
entirely missing on the mouthpiece side	24.9 \pm 0.8
entirely missing on the right side	26.0 \pm 0.3

Results from this study demonstrate that a partially or entirely missing (b) (4) has negligible impact on aerosol temperature emitted from the mouthpiece of the device.

VI. Recommendation

The sponsor has adequately addressed the remaining two device/engineering related issues (characterizing total mass of drug delivered to lungs and worst case evaluation of heat package failure). At this time, there are no more device/engineering related issues.

Please request Alexza to address the human factors concerns as recommended in Lt. Nguyen's memo.



Nayan Patel, Reviewer

11/4/11
Date




Sugato De, Combination Products Team Lead

11/4/11
Date



Lex Schultheis, Branch Chief

11/4/11
Date



Kwame Ulmer, Deputy Division Director

11/4/11
Date



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: November 1, 2011
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
TO: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
SUBJECT: NDA 022549 Staccato Loxapine – Inhalation (Psychiatric Patients)
CTS Consult: CON118063- Human Factors/Usability Review

Per your request, I have reviewed the Human Factors information pertaining to the proposed product. Please request the sponsor to provide additional information for the concerns outlined in the recommendation section, page 13.

Review Memo - Table of Content

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Evaluation of Human Factors Information

Overview

The Division of Psychiatry Products (CDER) has requested a consult from CDRH regarding the review of an NDA submission, # 022,549, Staccato Loxapine manufactured by Alexza Pharmaceuticals, Inc. This is a re-submission based on the Agency's Complete Response letter issued 10/6/2011. The CR letter consisted of a request for a human factors validation study along with two other requests for device performance testing.

For this resubmission, Nayan Patel is the device lead reviewer and he has consulted this reviewer to evaluate the Human Factors information provided in the submission. This review will focus on the sponsor's response to the Human Factors request.

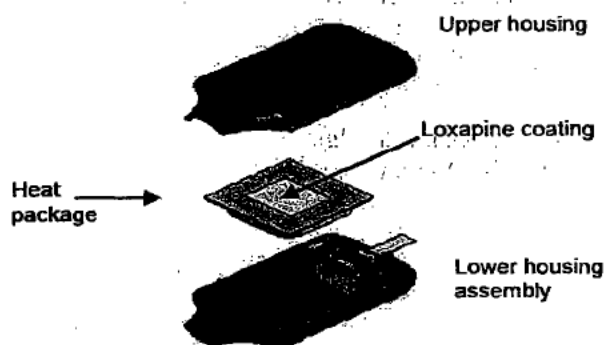
Device Description

Staccato® Loxapine for Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg.

Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza. Oral inhalation through the 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 rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

Staccato Loxapine (5 mg and 10 mg) has been developed 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.

Figure 1. Schematic of Staccato Loxapine



Note: Pouch not shown in schematic. (b) (4) are processing aids that are evaporated during drug product manufacturing.

Intended Use

The proposed combination product is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder.

Summary of Human Factors Information

The sponsor submitted Human Factors test protocol and report in the resubmission of the NDA. The following paragraphs outline the CDRH HF request and evaluation of the HF information provided in the resubmission.

CDRH's Human Factors Request

1. Based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, a prominent visible flash, and elevated inspired air temperature. These phenomena caused a startle response in some cases, which resulted in incomplete inhalation. Under these conditions, patients unfamiliar with the device may discontinue inhalation and, therefore, not receive the full, intended dose. CDRH requests that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting.

You must address the following:

- a. A human factors validation report that includes:
 - i. A detailed analysis of use performance and subjective data;
 - ii. Evaluation and documentation of user performance, use errors and task failures
 - iii. An evaluation of the effectiveness of proposed mitigation strategies (training, device labeling, etc.) through simulated use scenarios;
 - iv. Discussion of how unanticipated failures can be handled; and
 - v. Discussion of any further mitigation strategies necessary and if further validation is necessary.
- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to safe use of the product. The study must evaluate feedback provided by test participants, which focuses on their ability to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
- c. You must conduct a thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients. This analysis should include the independent and integrated aspects of both the device and user interactions. The risk analysis should address whether the device is used in ways that were not anticipated, especially if the device use environment affects device utility and user comprehension. This risk analysis should also include a discussion of the mitigations against use-related risks, and it should evaluate the effectiveness of the mitigations, based on the human factors validation study results.

Evaluation of Sponsor's Response to HF Request

In the resubmission, the sponsor provided a red-line HF protocol based on previous correspondences/meetings with the Agency and the final HF validation study report.

Summary of Findings from HF Report

Intended device users, uses, use environments, and training

Staccato Loxapine has been developed for the treatment of agitation associated with schizophrenia or bipolar disorder in adults. The administration of *Staccato* Loxapine to patients is intended to be supervised by a healthcare provider (HCP) in a healthcare setting such as an emergency department of a hospital, an in-patient psychiatric ward, a psychiatric emergency service, or a psychiatrist's office.

HCPs would prepare the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients will only be responsible for following the HCP's instructions in order to actuate the device and inhale the drug. Patients will not be responsible for reviewing the instructions for use, for preparing the device, for determining when the device is ready to use, or for determining if the device has actuated.

A wide range of HCPs working in various clinical environments are expected to administer *Staccato* Loxapine. For example, users might include Registered Nurses (RNs), Licensed Practical Nurses (LPNs), and physicians working in general hospital units, emergency departments, and psychiatric units or clinics.

No training on the instructions for use is expected for these users prior to device use; however, the instructions are presented in both the Full Prescribing Information for the product and the pouch label.

Device user interface

The user interface consists of the following elements:

- A pull tab, which is used to prepare the product for use after being removed from the pouch
- An indicator light (a green LED) which indicates whether the device is ready to be used or has already been used
- A mouthpiece for the patient to put in their mouth and inhale through

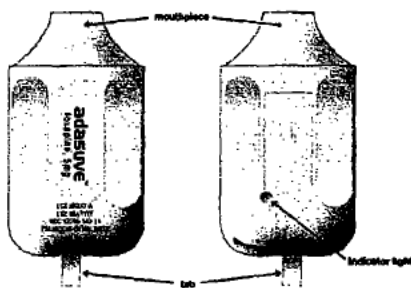


Figure 1. Images of the *Staccato* Loxapine device highlighting the user interface elements.

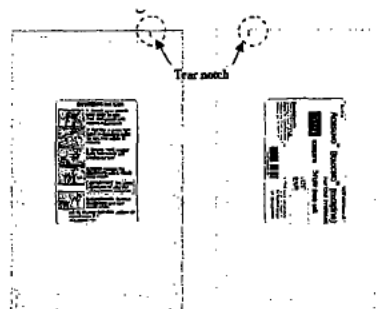


Figure 2. Images of the pouch for *Staccato* Loxapine. The tear notch is highlighted by the arrow pointing to the circle.

In addition to these elements on the device itself, the pouch has a tear-notch to facilitate opening the pouch and removing the device at the time of use. The pouch is illustrated below in Figure 3.

The use of *Staccato* Loxapine consists of the following operational steps:

- The HCP opens the pouch to remove the device
- The HCP removes the tab to activate the device for use and observes the illumination of the green LED indicator to confirm that the device is ready for use
- The HCP provides inhalation instructions to the patient
- The patient follows the inhalation instructions given by the HCP
- The HCP confirms the delivery of the dose by checking that the LED has turned off

Note that the HCP is the user primarily responsible for ensuring that the device is prepared properly and that the dose is administered properly. The patient is only responsible for following the HCP's instructions to actuate the device and inhale the drug. Instructions for use are provided with the device both as a part of the Full Prescribing Information and as a label on the back of the device pouch.

User task selection, characterization and prioritization

- Risk analysis methods
- Use-related hazardous situation and risk summary
- Critical tasks identified and included in HFE/UE validation tests

Summary of formative evaluations

Formative usability evaluations included studies to evaluate the device inhalation resistance (effort required to achieve a certain inhalation flow rate) and the actuation reliability of the device, along with an evaluation of published literature on the usability of similar devices.

Other findings from the clinical studies indicated that having more than one attempt to actuate the device is not problematic, as there were occasional reports of subjects and patients attempting multiple inhalations. Feedback from the clinical development program was also informative for the product design.

Most of the usability-related observations made during the clinical studies indicated that the root causes were identified and corrected. Other observations were considered to be indicative of the following two potential use errors:

- Inadequate inhalation
- Failure to recognize use state

The potential harms related to inadequate inhalation are a missed or delayed dose, or underdose which all have a minor severity impact. The potential harms related to a failure to recognize use state are a missed dose, a delayed dose or inappropriate administration of a second dose (in the case of a failure to recognize that the first dose was delivered).

The sponsor indicated that harms related to a missed dose or delayed dose are minor in severity. Harms related to inappropriate administration of a second dose could potentially have a serious safety impact. However, in the course of the clinical development program, there were no

instances in which subjects received a second dose inappropriately. In addition, in consideration of the combination of potential harm and probability of occurrence for these potential use errors results in a level of risk that is considered acceptable.

Validation testing

The purpose of the testing was to validate the use-safety and usability of *Staccato* Loxapine and the associated Instructions for Use. Representative users (healthcare providers and patients) interacted with the device in a simulated-use environment. These environments were chosen so that "challenge scenarios" could be evaluated that might not occur naturally in a clinical study. In order to simulate the environmental aspects of a healthcare setting that could affect dose administration, ambient background noise typical for such a setting were present during the test sessions.

In the initial summative HF study, 15 HCPs, representative of the physicians and nurses were enrolled. For the patient arm of the study 16 non-agitated individuals with schizophrenia and 16 non-agitated individuals with bipolar disorder participated in the study. Both sets of representative patients were required to have been treated for agitation in a healthcare setting at least once in the past. This initial study identified modifications that needed to be made to the pouch and the IFU for the HCP. A supplemental HF study was conducted with another 15 HCPs to revalidate the changes.

The HCPs performed 10 tasks in the initial study and 6 directed tasks in the supplemental study, most of which involved scenarios that challenged HCPs' ability to direct use of the device (e.g. intentionally defective devices or non-compliant standard patients). The representative patients in the initial study participated in 5 directed tasks, each of which involved normal use of the device. Two distractions were introduced during the representative patient directed tasks to challenge their ability to follow the HCP directions during the distraction. These tasks were chosen to be representative of either previously observed issues in the clinic or potential issues identified in risk analyses and were intended to comprehensively assess the use-safety of the device.

Because the preparation and use of *Staccato* Loxapine involves several steps, each directed task for each participant consisted of a full dosing scenario, i.e., starting with preparing the device for use and finishing with dose administration. The exceptions to this are some of the "challenge" scenarios where intentionally defective devices were presented to HCPs.

(b) (4)

Discussion and implications for additional risk mitigation

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, Alexza has undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. They changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP were unaware to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

(b) (4)



While the Agency recognizes that Alexza has taken helpful measures in its effort to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that Alexza to take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Improvements should be demonstrated through focused HF/usability validation.

Recommendations

Please request Alexza to address the following concerns:

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, you have undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. You changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP were unaware to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

(b) (4)

While the Agency recognizes that you have taken helpful measures to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

CDRH Human Factors Review Addendum

QuynhNhu Nguyen (CDRH) met with Yelena Maslov and Zachary Oleszczuk (CDER/DMEPA) to discuss findings from the HF validation study and consolidate comments from both review groups.

Please see the following revised recommendation on the HF validation study.

Recommendations

Please request Alexza to address the following concerns:

The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, you have undertaken helpful measure to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. You changed the location where the pouch can be opened so the device can be removed safely, and modified the content of the IFU to clarify instructions and information related to difficulties observed in the testing. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP were unaware to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

(b) (4)



While the Agency recognizes that you have taken helpful measures to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

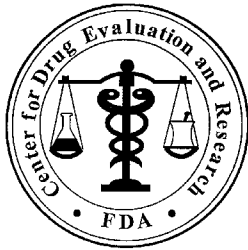
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/s/

KIMBERLY S UPDEGRAFF

11/10/2011

Intercenter Consult Review entered into DARRTS for the CDRH review team.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 3, 2011

To: **Thomas Laughren, M.D.**, Director
Division of Psychiatry Products (DPP)

Robert Levin, M.D.
Division of Psychiatry Products (DPP)
Office of Drug Evaluation I, OND, CDER

Through: **Solomon Iyasu, M.D., M.P.H.**, Director,
Division of Epidemiology I

Simone P. Pinheiro, Sc.D., M.Sc., Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: **Cary Parker, M.P.H.**, Epidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: Review of draft observational study protocol synopsis
entitled, "A Post-Marketing Observational Study to Evaluate
the Safety and Effectiveness of Staccato Loxapine in Agitated
Patients with Schizophrenia or Bipolar Disorder Treated in
Real World Emergency Settings."

Drug Name(s): ADASUVE (loxapine) Inhalation Powder (Staccato loxapine)

Submission Number:

Application Type/Number: NDA 022549

Applicant/sponsor: Alexza Pharmaceuticals, Inc.

OSE RCM #: 2011-3482

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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1 BACKGROUND/HISTORY

On December 11, 2009, Alexza Pharmaceuticals, Inc. (Alexza) submitted NDA 022549 to support the approval of *Staccato*® Loxapine (Adasuve®) for oral inhalation as a prescription drug product for the treatment of acute agitation associated with schizophrenia or bipolar disorder in adults. This product introduces a new medical delivery system for Loxapine. *Staccato* Loxapine is a single use, hand held device product that provides rapid systemic delivery of Loxapine through absorption in the lung. Due to the primary safety concern of pulmonary toxicity, the Division of Psychiatry Products in the Office of New Drugs (DPP/OND) issued a Complete Response Action Letter on October 8, 2010, and subsequently held an End of Review Meeting on December 17, 2010 and a Type C Meeting on April 29, 2011.

On August 4, 2011, the sponsor provided a resubmission of NDA 022549, including a proposed risk management plan to address the primary safety concern of pulmonary toxicity.

The proposed risk management plan consisted of three parts:

- a. Updated draft labeling – The prescribing information includes a boxed warning describing the risk of bronchospasm, patients who should not be treated with ADASUVE, the need to observe patients after treatment and to have a short-acting bronchodilator beta-agonist bronchodilator readily accessible. A contraindication is included for patients with acute respiratory signs/symptoms (e.g., wheezing) or who are taking medications to treat asthma or COPD;
- b. A proposed REMS that includes a Medication Guide, a multi-component communication plan, and an Element to Assure Safe Use (ETASU);
- c. An observational study protocol synopsis entitled, “A Post-Marketing Observational Study to Evaluate the Safety and Effectiveness of *Staccato* Loxapine in Agitated Patients with Schizophrenia or Bipolar Disorder Treated in Real World Emergency Settings.”

The sponsor’s updated draft labeling and proposed REMS are being reviewed by the Division of Risk Management in the Office of Surveillance and Epidemiology (DRISK/OSE).

DPP requested input from the Division of Epidemiology I in the Office of Surveillance and Epidemiology (DEPI-I/OSE) on the observational study protocol synopsis mentioned above. As a fully developed study protocol is not available at this time, only a *high level review* of the study synopsis is provided at this time. A fully developed protocol should be submitted by the Sponsor for the Agency to determine whether the proposed study can be used to support regulatory decisions.

2 SYNOPSIS OF PROPOSED EPIDEMIOLOGICAL STUDY

The study synopsis describes a post-marketing observational study with the following objectives: 1) to assess the occurrence and nature (e.g., severity) of serious adverse events (SAEs) and adverse events (AEs), with a primary focus on respiratory

AEs, experienced following the administration of *Staccato* Loxapine in an emergency setting; 2) to compare the frequency of AEs and SAEs for *Staccato* Loxapine vs. anti-psychotic and/or benzodiazepine medications administered intramuscularly used in the acute treatment of agitated patients; 3) to describe the practice patterns for the use of *Staccato* Loxapine in an emergency setting; 4) to evaluate the effects of different treatments for agitation using the Positive and Negative Symptom Scale-Excitement Component (PANSS-EC).

The proposed study is a multi-center, non-randomized prospective observational cohort study to be conducted at approximately 50 medical or psychiatric emergency settings in the U.S. with an estimated enrollment period of 18-24 months. Patients will be eligible for this study if they have a diagnosis of schizophrenia or bipolar disorder who require treatment for agitation (voluntarily or involuntarily) as determined by the investigator. The sponsor proposed the following inclusion criteria: 1) patients are 18 years or older at study entry; 2) patients with schizophrenia or bipolar disorder as determined by the investigator requiring anti-psychotic (IM or aerosol) and/or IM benzodiazepine treatment for agitation in medical or psychiatric emergency settings; 3) patients (or legal representatives) willing and able to provide written informed consent (either at the time before dosing or following treatment after agitation has subsided). The following patients will be excluded from the study: 1) patients diagnosed with dementia; 2) patients ineligible to receive *Staccato* Loxapine according to the approved Prescribing Information and the approved product REMS (e.g., those who have acute respiratory signs/symptoms or who are currently being treated for asthma or COPD will not receive *Staccato* Loxapine).

Outcome data on safety will be collected up to 24-hours post-treatment or until discharge/transfer from the emergency department, whichever comes first. Outcomes include: 1) respiratory AEs (e.g., respiratory signs and symptoms such as coughing, wheezing, or shortness of breath); 2) use of short-acting bronchodilator or other medication to treat emergent symptoms (e.g. bronchospasm, extrapyramidal symptoms); 3) other AEs (including AEs of interest such as sedation/somnolence, extrapyramidal symptoms); 4) SAEs. The sponsor also proposes assessment of treatment patterns and effectiveness: 1) baseline PANSS-EC scores for patients treated with *Staccato* Loxapine compared with patients treated with other anti-agitation medications; 2) mean change in PANSS-EC score from baseline to 1 h post-treatment (or at discharge if earlier than 1 h); 3) usability of *Staccato* Loxapine including the number (and percent) and characteristics of patients who refused or were unable to use *Staccato* Loxapine when it was offered; 4) physician treatment choices for treating agitation in an emergency setting; 5) doses of all anti-agitation medications administered (medication, dose, route of administration, timing) up to 24 h from first dose of study/comparator drug administration (or at discharge from emergency service if earlier); 6) physical restraints used, if any; 7) security personnel or dedicated staff (“sitters”) assigned to patient post dosing, if any; 8) availability of patient medical/medication history and physical examination results prior to *Staccato* Loxapine treatment. Other additional data proposed to be collected included: 1) demographics of patients treated with *Staccato* Loxapine compared with patients treated with other anti-agitation medications; 2) agitation triggers; 3) medical information

regarding the current emergency visit (diagnoses/comorbidities); 4) information on respiratory history, including presence or absence of COPD, asthma, former and current smoking, past and current treatment for respiratory problems; 5) other concomitant medications (type of medication, indication, dose, duration, frequency). Additionally, patients who receive at least one dose of IM or inhaled medication for the treatment of agitation will be included in the evaluation for safety. All AEs and SAEs will be recorded from the time the patient signs the informed consent (or from the time of dosing if informed consent is obtained post-dosing) until end of the study period.

Sample size estimations were based on the precision (half the width of the confidence interval [CI]) for the estimated AE rates in persons receiving *Staccato* Loxapine. The rate of respiratory AEs in emergency room settings were assumed to be 3 times higher (i.e. 2.4%) than what was observed in the *Staccato* Loxapine Phase 3 program (0.8%), which employed respiratory exclusion criteria similar to those described in the *Staccato* loxapine Prescribing Information. Given a sample size of 600 patients receiving *Staccato* Loxapine, the estimated precision for the observed respiratory AE rate in persons receiving *Staccato* Loxapine was estimated to be $\pm 1.2\%$. For comparison purposes, it was estimated that the study will need to enroll approximately 800 patients receiving other IM anti-psychotics and/or benzodiazepines.

Proposed analyses were descriptive and inferential in nature. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by incidence, severity grade, and relationship to study drug. The frequency and percentage will be calculated for patients reporting AEs (e.g. respiratory AEs) and SAEs. Analyses comparing changes in scores of PANSS-EC between patient subgroups will be performed by means of ANCOVA and 95% CIs will also be calculated. ANCOVA models will be fitted using type III sums of squares and adjusted least square means will be computed.

3 DEPI COMMENTS

Importantly, only a brief summary of the proposed study is provided in the study synopsis submitted by the sponsor. Therefore, only *high level* comments regarding this proposed study can be provided at this time by DEPI. If the drug is approved for marketing, a fully developed protocol should be submitted by the sponsor for review and approval by the Agency prior to study initiation. DEPI suggests that the sponsor refers to the principles outlined in the draft guidance for pharmacoepidemiologic studies when developing the study protocol, which can be found at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>

DEPI's general comments on the study synopsis are provided below.

In general, the study objectives are reasonable. A rationale for the study setting and the criteria to be employed in the selection of study sites should be detailed in the study protocol. The study population should reflect the population receiving this product in the real world setting as closely as possible. Inclusion and exclusion criteria should be detailed in the study protocol. In particular, inclusion and exclusion criteria that rely on patients' availability of medical history or ability to report medical history reliably should be addressed. For example, this study proposes to include patients with a

diagnosis of schizophrenia or bipolar disorder who require treatment for agitation in psychiatric emergency settings in the U.S. Patients diagnosed with dementia, as well as those with acute respiratory signs/symptoms or those currently treated for asthma or COPD, will be excluded from the study. However, some of these patients may enter the medical or psychiatric emergency settings without a formal diagnosis, have undiagnosed disease, may be unable to provide a reliable medical history or may not have medical history readily available. The sponsor should provide details regarding how medical diagnosis or medical history will be determined for all patients and how inability to determine diagnosis or medical history in some patients may impact the interpretability of study findings. Moreover, information regarding the generalizability of patients actually included in the study to the population of patients receiving *Staccato* Loxapine in real world settings should be discussed.

The study design and analyses should minimize potential for surveillance bias, due to differential assessment and follow-up between study groups, and bias due to lack of comparability between study groups. This study proposes that patients with a diagnosis of schizophrenia or bipolar disorder treated for agitation with IM anti-psychotic and/or benzodiazepine medications as the comparator group. It can be argued that patients who are given *Staccato* Loxapine may be significantly different from the patients who receive the other IM drugs. Theoretically, results may be biased in favor of *Staccato* Loxapine patients if this medication is more likely to be given to healthier patients (i.e. patients who are able to and compliant with the use of the inhalation device and who do not have a history of asthma or COPD). The sponsor should address the comparability of the study comparison groups as well as how any differences between study groups will be handled, including specifying important confounders and how these would be handled in the analyses. Additionally, the sponsor should discuss whether differential follow-up (e.g. if patients on a particular study group are more likely to be discharged home prior to 24 hours post medication administration) will impact interpretability of study findings and provide strategies to minimize/eliminate these discrepancies.

Additionally, standard, case definitions of all AEs and SAEs should be provided in the study protocol, including operational definitions for the respiratory outcomes of interest. Importantly, the protocol should describe the method of outcome assessment across study groups, including frequency of assessment/s and the required expertise/training of medical team performing the assessment/s of the outcomes of interest (e.g. auscultation of lung sounds may require trained medical professionals).

Detailed sample size calculations for each outcome should be provided for each outcome. In addition, information regarding the reliability of the assumptions concerning background rates of respiratory AEs should be provided (e.g. reference from literature or information from pilot studies).

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/s/

CARY C PARKER
11/03/2011

SOLOMON IYASU
11/03/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Anesthesiology and Respiratory Device Branch (ARDB)
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGID)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RESPONSE TO CONSULT REQUEST

Date: September 22, 2010

From: QuynhNhu Nguyen, Biomedical Engineer, Anesthesiology and Respiratory Device Branch,
Division of Anesthesiology (ARDB), General Hospital, Infection Control, and Dental
(DAGID), CDRH

Through: Lex Schultheis, M.D., Ph.D, ARDB Chief, DAGID/ODE/CDRH
Jim Robotham, M.D., Clinical Deputy Division Director, DAGID/ODE/CDRH
Kwame Ulmer, M.S., Deputy Division Director - Science and Policy, DAGID/ODE/CDRH

To: David Claffey, Ph.D, Division of Psychiatry Products, CDER
Kimberly Undegraff, RPh, MS, RAC, Senior Regulatory Project Manager
Thomas Laughren, M.D., Division Director, Division of Psychiatry Products, CDER

Re: NDA 022549 Alexza Staccato Loxapine for Treatment of Agitation

Consult Requests

The Division of Psychiatry Products has received a new NDA from Alexza Pharmaceuticals supporting the use of Staccato Loxapine for Inhalation for the treatment of agitation in patients with schizophrenia and mania of bipolar disease. CDRH was consulted several times during the Pre NDA process and Sugato De provided comments & guidance regarding the NDA submission.

The filing meeting was scheduled for January 21, 2010. The submission is electronic and can be found at the following link: \CDSESUB1\EVSPROD\NDA022549\022549.enx.

Thomas Oliver, Pharmaceutical Assessment Lead, is requesting this consult. The CMC reviewer is David Claffey, Ph.D.

The consult request included:

1. Determine whether the device manufacturing and performance is acceptable from a CDRH (engineering) view point. In particular, whether the components of the device such as the heat package, ^{(b) (4)} and breath sensor mechanism & housing are adequately robust for commercial use & whether the in-process and release controls for their manufacture are adequate.
2. Determine whether the changes made between the first commercial version and the final commercial version will have any impact on the functionality and robustness of the device from an engineering perspective.

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1 EXECUTIVE SUMMARY

1.1 CDRH DAGID ARDB RECOMMENDATION

From a device review perspective, a complete response to outstanding deficiencies is needed before this combination product may be considered safe and effective. Specifically, the patients treated are likely to be agitated psychiatric patients in an emergency room. This health care setting raises efficacy questions that may be particularly related to the usability of the device because the product was not studied in this environment. Furthermore, the pulmonary symptoms reportedly associated with the device among patients may be in-part related to the location of drug particle deposition in the airways. However, the respirable dose of drug product was not completely characterized, so that etiology of reactive airways event could not be fully understood to evaluate product safety. In addition, manufacturing and process-related deficiencies identified by the inspection team pose concerns because they appear likely to impact safety and effectiveness of the final product. Finally, the model utilized by the sponsor to evaluate the potential risk of catastrophic failure of heat package integrity was unrealistic and may underestimate the potential injury to patients in the event of a serious manufacturing defect.

A complete response to the following deficiencies is recommended before Staccato Loxapine be considered approvable from a device perspective.

1. Device Effectiveness and Safety: A human factors validation study is recommended for the device to be marketed

(b) (4)

based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, visible flash, and elevated inspired air temperature. Under these conditions, patients unfamiliar with the device may discontinue inhalation, or may be more difficult to accept the inhalation. CDRH recommends that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting. Evaluation of human factors should be in a study designed for this express purpose and include:

- a. A human factors validation report that includes:
 - o a detailed analysis of use performance and subjective data;
 - o documentation of use errors and task failures;
 - o an evaluation of the effectiveness of proposed mitigations (training, device labeling, etc.) through simulated use scenarios;
 - o discussion of how unanticipated failures can be handled; and
 - o discussion of any further mitigation necessary.
- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to use safety and evaluation of the device feedback provided by test participants which focuses on how they are able to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
- c. A thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients is required. This analysis should include the independent and integrated aspects of

both the device and user interactions. It should be noted if the device is being used in ways that were not anticipated; especially if the device use environment affects device utility and user comprehension. This risk analysis should also include discussion of the mitigations to use related risks and the effectiveness of each mitigation based on the human factors validation study results.

2. Device Safety: Quantitative relation of the respirable dose of the drug product to inhaled particle size is recommended

(b) (4)



3. Preapproval Inspection of Manufacturing Site Alexza Pharmaceutical – resolution of the following deficiencies is recommended from a device performance’s standpoint

(b) (4)



4. Heat Package Worst Case Testing was inadequate- more realistic testing of a serious manufacturing defect is recommended

The worst case simulation test that was conducted during product development consisted of 1 mm holes, which were drilled in specific areas of the heat package. However, CDRH requests that a more realistic test be conducted, such as failure of (b) (4) along a seam that normally holds the tray and the lid together. This type of simulation is expected to more pragmatically replicate a possible manufacturing defect. The purpose of the heat package worst case simulation to evaluate catastrophic heat package failure was to anticipate potential injury to a patient when making a risk benefit determination for a product. To understand the potential risk to patients, please conduct a more realistic worst case testing with temperature measurements inside an anatomical model of the upper airway during simulated inspiration.

1.2 SUMMARY OF REVIEW

The evaluation conducted by CDRH is comprised of two parts: performance verification and validation; and manufacturing processes and controls. Performance verification and validation measures were conducted by the Office of Device Evaluation on the product to be commercialized. Manufacturing processes and controls were conducted by Office of Compliance.

Device Performance Verification and Validation

Method of Review

In order to evaluate the safety and effectiveness from the viewpoint of verification and validation measures, CDRH ODE conducted a review of:

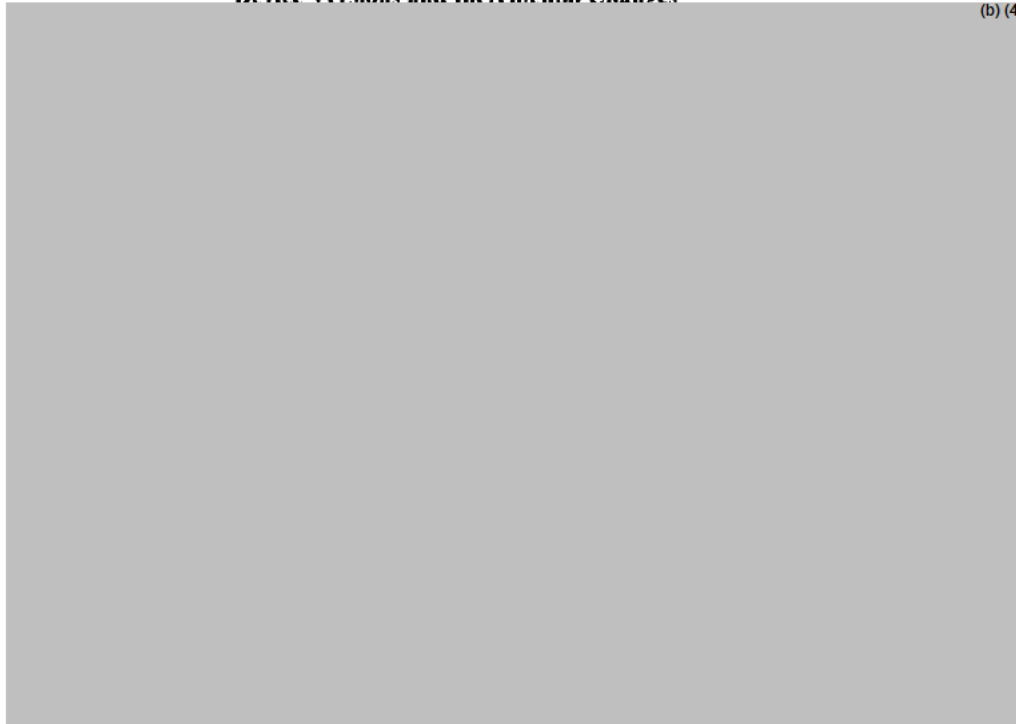
- Product designs, specifications, and modifications
- Sterilization/Shelf-life/Reuse
- Biocompatibility
- Software information
- Electromagnetic compatibility, electrical, mechanical, and thermal safety
- In-vitro performance testing
- Sterilization/shelf life/reuse
- Reliability
- Risk analysis
- Device actuation study
- Device labeling

Summary of Findings

Considerable modifications were made throughout the development of the product and are documented in the following diagram.

Device Versions and Incremental Changes

(b) (4)



There were a total of five device versions during product development: Clinical Version 1, Clinical Version 2, Commercial Version 1, Commercial Version 2, and Commercial Version 2.1. Detailed discussions of each of the modifications can be found in the Review Discussion and Comments, and Appendix of this review memo. Verification and validation assessments were conducted by the sponsor using a step-wise approach, and all assessments were not conducted on the final commercial version: Commercial Version 2.1.

Due to major changes to many of the device components between Clinical Version 2 and Commercial Version 1, Alexza has provided comparative in-vitro performance testing along with bioequivalence and stability studies, which were conducted and served as a bridge between these two versions. It should be noted that phase 1, 2, and 3 clinical trials were conducted on Clinical Version 2; whereas in Commercial Version 2, small targeted clinical studies were conducted to answer specific questions. These targeted studies evaluated smokers PK, QTc, Asthma, and COPD patients. Also, an actuation reliability study, product characterization studies and registration stability studies were conducted with Commercial Version 2. The differences between Commercial Version 2 and Commercial Version 2.1 do not impact the aerosol performance of the product.

While there were many evolutionary changes during the development of the product, my review evaluated verification and validation testing that was conducted on the finished products. The following provides a brief summary of the testing and results:

o *Comparative in vitro data between device versions*

This was evaluated to evaluate possible differences between the various device versions, in particular Clinical Version 2 and Commercial Version 1. Key performance parameters of emitted dose content uniformity, aerosol particle size distribution and aerosol impurities were specifically compared. The results indicated the two device versions are comparable. In addition, the two device versions were evaluated to compare two important user interface characteristics – the inspiratory resistance of the device and the performance of the breath actuation mechanism. Inhalation resistance was tested as

part of design verification testing for the commercial version. Pre-defined inhalation resistance acceptance criteria, consistent with the clinical version performance, were met. The breath actuation mechanism for the Commercial Version consists of a simple electro-mechanical flow switch designed to actuate at approximately the same flow rate as the Clinical Version.

○ *Other device specific tests compared the Commercial Version 1 to recognized standards*

These included electromagnetic compatibility and electrical safety, which were conducted on commercial version 1 in accordance with FDA's recognized consensus standard, IEC 60601-1, and 60601-2, General requirements for basic safety and essential performance, and requirements and tests standard. All test results were found acceptable.

○ *Biocompatibility of the device was reviewed*

Tests including cytotoxicity, sensitization, irritation, and systematic toxicity were conducted on Commercial Version 2. All four test reports demonstrated acceptable results. In addition to the four biocompatibility evaluations, testing for foreign particulates evaluation, extractables/leachables, and potential trace metal impurities in the aerosol were also conducted, which were evaluated by CDER. The results were found acceptable.

(b) (4)

○ *Sterilization*

The applicant evaluated leachable materials through various registration stability program at 6 month time frame at 25 °C and 40°C storage condition. Their findings indicated that the results can be extrapolated for a desired shelf-life is (b) (4). The device is indicated for single use so repeat sterilization was not evaluated.

○ *Device reliability assessment*

This review was based upon a series of device actuation studies. While there were 2 failures reported during in-vivo use, and 4 failures reported during in-vitro use, no failures appeared to pose a direct safety risk to the patient, so the overall reliability rate of the product was demonstrated to be acceptable.

○ *Risk management procedures*

Alexza's procedures are in accordance with *ISO 14971*, as referenced above, with additional input from the drug product guidance *ICH Q9: Quality Risk Management*. From a device operational standpoint, the risk analysis was found acceptable.

○ *Human factors validation*

No study was conducted on the final product version using representative device users and healthcare providers in the intended environment of use. This is a deficiency that may impact understanding of effectiveness in the emergency room setting.

○ *Device labeling*

Suggestions from this reviewer with specific comments can be found in section 8 of this review memo.

Summary Recommendation: A complete response to deficiencies in validation and verification outlined above is recommended before the combination product may be considered approvable from a device evaluation perspective.

Manufacturing processes and controls review by the CDRH Office of Compliance

CDRH's Office of Compliance, David Dar, was consulted to review the manufacturing portion of the submission. Based solely on the written information submitted in the application, the manufacturing section appeared to be adequate.

A preapproval inspection of the final product assembly site, Alexza's site was also conducted on August 2010. The focus of interest for CDRH and for CDER was the heat package, which according to FDA regulation; CDRH is not authorized to conduct an on-site inspection of the component of the product. Therefore, the preapproval inspection conducted at Alexza's site evaluated procedures, and verified that standards of component acceptance by the manufacturer were adequate. The Preapproval inspection conducted revealed 10 notable findings.

A copy of the (#483) inspection report was forwarded to CDRH for review. While CDRH's Office of Compliance is currently reviewing this information to determine the impact of these observations on their overall assessment of manufacturing adequacy, my interpretation from the standpoint of CDRH's Office of Device Evaluation, is that four of these ten observations/findings are likely to have a direct impact on the performance data (safety and effectiveness) of the device. My recommendations are outlined above and described in the body of this review.

At this time, the recommendation from CDRH's OC is still pending.

1.3 ACTION ITEMS TO BE INCLUDED IN THE COMPLETE RESPONSE LETTER

1.  (b) (4)

Furthermore, based on device sample testing conducted with the review team at CDRH, actuation of the device was associated with a loud pop, visible flash, and elevated inspired air temperature. Under these conditions, patients unfamiliar with the device may discontinue inhalation, or may be more difficult to accept the inhalation. CDRH requests that a human factors validation study be conducted with representative healthcare providers and patients to validate that the product can be used effectively in the proposed clinical setting.

Please address the following:

- a. A human factors validation report that includes:
 - i. A detailed analysis of use performance and subjective data;
 - ii. Documentation and evaluation of use errors and task failures
 - iii. An evaluation of the effectiveness of proposed mitigations (training, device labeling, etc.) through simulated use scenarios;
 - iv. Discussion of how unanticipated failures can be handled; and
 - v. Discussion of any further mitigation necessary.

- b. The study should be designed to include meaningful evaluation of user performance on tasks that are critical to use safety and evaluation of the device feedback provided by test participants which focuses on how they are able to perform these tasks. For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.
 - c. A thorough analysis of use-related hazards that could lead to potential risks to health care providers and patients is required. This analysis should include the independent and integrated aspects of both the device and user interactions. The risk analysis should note if the device is being used in ways that were not anticipated; especially if the device use environment affects device utility and user comprehension. This risk analysis should also include discussion of the mitigations to use related risks and the effectiveness of each mitigation based on the human factors validation study results.
2. According clinical studies conducted with patients who had reactive airway diseases (Asthma, and chronic obstructive pulmonary disease) showed that there were clinically significant reductions in FEV₁ among patients with asthma who were treated with Staccato Loxapine. These clinically significant reductions appear to have been dose-related.

Patients with chronic obstructive pulmonary disease were also at increased risk compared to the general FEV₁ population. We acknowledge that it may not be possible to pre-identify patients at increased risk for airway reactivity provocation when they present with agitation in an emergency care setting. The site of deposition for inhaled particles and the intrapulmonary dose fraction may be related to the observed reduction in FEV₁.

Please address the following:

(b) (4)

3. CDRH requests that resolution of the following Preapproval Inspection deficiencies be addressed to adequately evaluate device performance. Please submit supporting documentations for review.

(b) (4)

(b) (4)



4. The worst case simulation test that was conducted during product development consisted of 1 mm holes, which were drilled in specific areas of the heat package. However, CDRH requests that a more realistic test be conducted, such as failure of (b) (4) along a seam that normally holds the tray and the lid together. This type of simulation is expected to more pragmatically replicate a possible manufacturing defect. The purpose of the heat package worst case simulation to evaluate catastrophic heat package failure was to anticipate potential injury to a patient when making a risk benefit determination for a product. To understand the potential risk to patients, please conduct a more realistic worst case testing with temperature measurements inside an anatomical model of the upper airway during simulated inspiration.

CDRH/CDER CONSULT REVIEW MEMORANDUM

2 MATERIALS REVIEWED

eCTD Original Application

Alexza Responses dated 1/27/2010, 2/3/2010, 5/27/2010, 7/12/2010

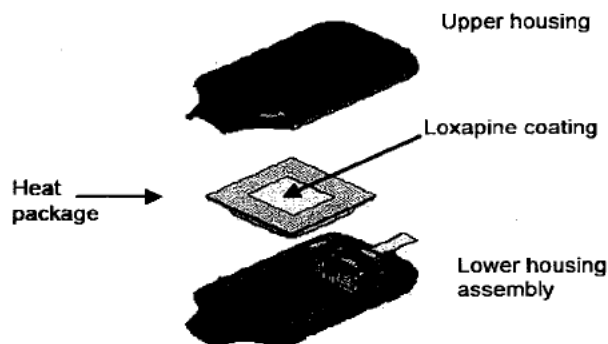
Amendments # 15, 17, 18 dated 7/19/2010, 8/20/2010, 8/31/2010

Intercenter/Combination Product Consults Request and Background Materials

3 BACKGROUND

The Division of Psychiatry Products (CDER) has requested a consult from CDRH regarding the review of an NDA submission, # 022,549, Staccato Loxapine manufactured by Alexza Pharmaceuticals, Inc. Staccato® Loxapine for Inhalation is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg. Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza. Oral inhalation through the 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 rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration. Staccato Loxapine (5 mg and 10 mg) has been developed 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.

Figure 1. Schematic of Staccato Loxapine



Note: Pouch not shown in schematic. (b) (4) are processing aids that are evaporated during drug product manufacturing.

Sugato De provided a consult dated November 20, 2008 for Alexza's IND, submission number 73,248. This review was conducted to evaluate in vitro data between the Phase 3 device and the updated device. The changes that were incorporated in the updated device were: (b) (4)

This consult concluded that in vitro comparability testing has demonstrated that the two versions of the device have comparable aerosol performance properties, including emitted dose, emitted dose content uniformity, aerosol particle size distribution and aerosol impurities. In addition, assessment of key user interface characteristics (the inspiratory resistance of the device and the performance of the breath actuation mechanism) also demonstrate the comparability between the two versions of the device. However, the review also identified three concerns for the updated device version: (1) evaluation for mechanical safety, electrical safety or electromagnetic

compatibility in accordance to IEC 60601-1: Medical Electrical Equipment General Requirements for Safety and with IEC 60601-1-2: Electromagnetic Compatibility Requirements and Tests; (b) (4)

(3)
complete test report, including protocols, acceptance criteria, results and conclusions for evaluating generation of (b) (4)

Subsequently, Alexza submitted the NDA, submission number 22,549. At the filing meeting, it was not clear to the review team how many device versions, clinical and commercial, are available. Based on additional information provided in the applicant's responses dated 1/27/2010 and 2/3/2010, the applicant clarified that there are two clinical versions: Clinical Version 1 and Clinical Version 2. Additionally, there are three commercial versions: Commercial Version 1, Commercial Version 2, and Commercial Version 3 (2.1). A fill-able decision was reached based on the information submitted in these two responses. Detailed review of the submission indicated that the applicant has conducted in vitro performance comparative testing for emitted dose, emitted dose content uniformity, aerosol particle size distribution, and aerosol impurities for Clinical Versions 1 and 2, and Commercial Versions 1 and 2; biocompatibility evaluation for Commercial Version 2; evaluation for mechanical safety, electrical safety or electromagnetic compatibility for Commercial Version 1.

4 PRODUCT INFORMATION

4.1 Indications for Use

The proposed combination product is indicated for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder.

4.2 Design/Specifications

Staccato® Loxapine for Inhalation (Staccato Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by oral inhalation of a thermally generated aerosol of loxapine. Staccato Loxapine is available in two doses: 5 mg and 10 mg. Staccato Loxapine is based on the proprietary Staccato delivery system developed by Alexza Pharmaceuticals, Inc. (Alexza).

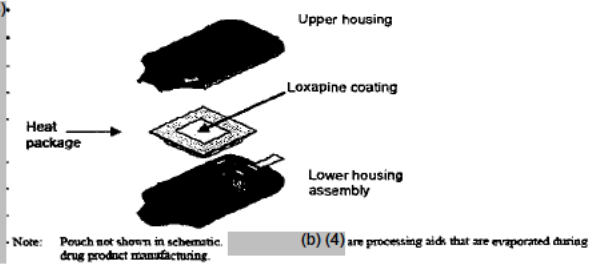
Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung.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

Staccato Loxapine (5 mg and 10 mg) has been developed 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. Currently available therapies for agitation have substantial limitations—namely, relatively slow onset of effect (oral and IM agents), pain from administration and risks to caregivers of needle stick injuries.

The composition of Staccato Loxapine is listed in Table 1 and shown schematically in Figure 1. Quality standards are noted for applicable components. There are no excipients in the drug product.

Table 1. Composition of *Staccato* Loxapine

(b) (4)

Figure 1. Schematic of *Staccato* Loxapine

The following list provides a list of critical components, which are defined by the Draft Guidance for Industry MDI/DPI Drug Products (October 1998) as: “Those [components] that contact either the patient (i.e., the mouthpiece) or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary protective packaging” (this is the definition for a dry powder inhaler, as the guidance does not specifically address drug products like *Staccato* Loxapine).

Critical Component	Reason for Criticality
Loxapine base	Active pharmaceutical ingredient (API)
Upper housing	Forms part of the mouthpiece, which comes in contact with the user and formulation
Lower housing assembly	Forms part of the mouthpiece, which comes in contact with the user and formulation Affects the overall performance of the device (activation and actuation mechanisms)
Heat package	Affects the overall performance of the device (heat source for formation of aerosol)
Pouch	Protective (primary) packaging

4.2.1 Critical Component # 1: Loxapine Base – Drug Substance - Deferred to CDER

4.2.2 Critical Component # 2 and 3: Upper and Lower Housing Description and Function

(b) (4)

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/s/

KIMBERLY S UPDEGRAFF

10/08/2010

Entering Interagency Consult Review from CDRH since the reviewer does not have access to DARRTS.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 27, 2010

TO: Thomas Laughren, MD
Director
Division of Psychiatry Products (DPP)

FROM: Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 8/27/10*
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-549, Staccato® Loxapine
Inhalation Aerosol, 5 mg and 10 mg, sponsored by
Alexza Pharmaceuticals, Inc.

At the request of the Division of Psychiatry Products (DPP), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study # AMDC 004-103
Title: "Bioequivalence of the Commercial Product Design (CPD) and the Current Clinical Version (CCV) of Staccato® Loxapine for Inhalation in Healthy Volunteers"

The clinical portion of this study was conducted at the Centre for Clinical Studies, St. Kilda Road Central Melbourne, Victoria, AUSTRALIA. Following the clinical inspection (7/19-22/2010), Form FDA-483 was issued (**Attachment 1**). A response from the Centre for Clinical Studies was received on August 24, 2010 (**Attachment 2**).

The analytical portion was conducted at [REDACTED] (b) (4). Following the inspection of the [REDACTED] (b) (4) Form FDA-483 was issued (**Attachment 3**). Response from [REDACTED] (b) (4) to the Form 483 has not been received as of the date of this writing. We will amend this memorandum if the response from [REDACTED] (b) (4).

changes our conclusion. Our evaluation of the inspectional findings and response from Centre for Clinical Studies follows:

Clinical Site - Centre for Clinical Studies, Melbourne, Victoria, AUSTRALIA

1. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, on visit 2 check-in Subject 14 reported they consumed alcohol, an item that was to be abstained from during the study. Additionally, the study personnel taking the history marked the "No" box. There is no indication this was observed, evaluated and/or corrected by an approved official during the study or post-study review.

On visit 2 check-in Subject 16 reported they consumed chocolate, an item that was to be abstained from during the study. The study personnel identified this deviation however, there is no indication this was communicated to the sponsor or other individual for evaluation of significance either during the study or post-study review.

On visit 2 check-in study personnel marked Subject 30's inclusion data as "no" although the answers should be yes for inclusion. There is no indication this was observed, evaluated, and corrected either during the study or post-study review.

At the 4 hour vital signs check during visit 2 Subject 31 had a BP in the source data of 98/59. The corresponding case report form has the BP recorded as 98/89. There is no indication that this error was observed, investigated or corrected during any review.

The response from the Centre for Clinical Studies states that protocol requirements were met for subject 14, since the subject tested negative for breath alcohol at the check-in. Similarly protocol requirements were met for subject 16 at the time of entry. The data should have been entered correctly for subjects 30 and 31. The OCP reviewer should determine if subject 14 should be excluded in the bioequivalence evaluation. DSI recommends that case records for subjects 30 and 31 are sufficient after these corrections.

2. Investigational drug disposition records are not adequate with respect to use by subjects.

Specifically, subject 23 was prescribed three doses of 5 mg drug. Source data records document the subject received two doses. The subject did not complete the study. Neither the source data records, the prescription or other record documents this dose as not having been administered. Clinic and pharmacy records do indicate one dose of 5 mg was returned unadministered without identifying the source.

Subject 25 was prescribed three doses of 10 mg drug. Source data records document the subject received two doses. The subject did not complete the study. Neither the source data records, the prescription or other record documents the dose as not having been administered and returned to the pharmacy. Clinic and pharmacy records do indicate one dose of 10 mg was returned unadministered without identifying the source.

The Centre for Clinical Studies responds that labels on the unused, returned devices contained the recorded treatment period and subject number. DSI recommends accepting the data from subjects 23 and 25.

Analytical Site - (b) (4)

1. Failure to fully evaluate dilution linearity of the loxapine assay. The concentrations of loxapine in 61 study plasma samples are higher than the dilution QC at 200 ng/mL loxapine.

(b) (4)

(b) (4)

DSI recommends that the accuracy of loxapine concentrations for these samples is questionable, and these data for loxapine assay should be excluded from the bioequivalence determination.

2. The quality control (QC) samples (0.150, 20.0 and 40.0 ng/mL) and calibration range (0.0500 to 50.0 ng/mL) for 7-hydroxy-loxapine or 8-hydroxy-loxapine used in the analytical runs were not representative of the 7-hydroxy-loxapine or 8-hydroxy-loxapine concentrations observed in study plasma samples. For example, the maximum concentrations observed in the study are 3.60 ng/mL for 7-hydroxy-loxapine, and 14.7 ng/mL for 8-hydroxy-loxapine, respectively.

Calibration standards were 0.0500, 0.100, 0.500, 5.00, 15.0, 30.0, 45.0 and 50.0 ng/mL for 7-hydroxy-loxapine or 8-hydroxy-loxapine in the analytical runs. The concentrations of mid QC (20.0 ng/mL) and high QC (40.0 ng/mL) were higher than the maximum observed concentrations 3.60 ng/mL for 7-hydroxy-loxapine, and 14.7 ng/mL for 8-hydroxy-loxapine. However, (1) the calibration curves were linear for 7-hydroxy-loxapine and 8-hydroxy-loxapine, (2) all mid QCs for both analytes passed, and (3) only 3 of 56 low QCs failed for 7-hydroxy-loxapine, and 8 of 56 low QCs failed for 8-hydroxy-loxapine in 27 accepted runs. DSI recommends accepting the data for 7-hydroxy-loxapine and 8-hydroxy-loxapine.

3. The Certificate of Analysis for the reference standard #2085 (Loxapine-d₈) requires storage (b) (4)
During the conduct of the study, this compound was stored in

(b) (4)

Reference standard was not necessarily stored at the recommended conditions. However, the deuterated analog (Loxapine-d₈) used as

an internal standard was stored under the same conditions. DSI is of the opinion that this observation is unlikely to have significant impact on the study outcomes.

Conclusion:

Following inspections of the clinical and analytical portions of Study AMDC 004-103, DSI recommends the following:

1. The OCP reviewer should determine if subject 14 should be excluded in the bioequivalence evaluation.
2. Accuracy of the reported plasma data for loxapine in Table 1 for Study AMDC 004-103 is not assured. The reported data for loxapine concentrations listed in the Table 1 should be excluded from the bioequivalence determination.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

Final Classification:

**VAI - Centre for Clinical Studies, Melbourne, Victoria,
AUSTRALIA**

VAI - [REDACTED] (b) (4)

cc: DARRTS
DSI/Ball/Haidar
DSI/Yau/Rivera-Lopez/CF
OND/ODEI/DPP/Kimberly Updegraff/Robert Levin
OTS/OCP/DCPI/Raman Baweja/Andre Jackson
HFR-PA3515/Barbara Rincon
HFR-PA350/Carol Gripp
HFR-SW250/Theressa Smith
HFR-SW250/Teena Aiken
Draft: XC 8/25/10
Edit: MFS 8/25/10, MKY 8/27/10
DSI: 6047
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FACTS: 1157507

cc: email
CDER DSI PM TRACK

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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/s/

XIKUI CHEN
08/27/2010

DATE: May 12, 2010

TO: NDA 22-549

FROM: David J. Claffey, Ph.D.

THROUGH: Christine Moore, Ph.D.

**SUBJECT: Considerations for Inspection (PAI) of Alexza Pharmaceuticals, Inc,
Mountain View, CA for NDA 22-549**

NDA 22-549 from Alexza Pharmaceuticals provides for Staccato (loxapine inhalation powder), a first-in-class drug/device combination. Although it shares many characteristics with marketed inhalation devices, it is unique in that the drug substance (loxapine) is coated on the outside of a heat package component whose outside surface heats to a target of 400°C (b) (4). The drug substance vaporizes and then condenses to an aerosol which is inhaled by the patient. To this reviewer's knowledge, this is the first proposed use of (b) (4) as part of a drug/device.

The purpose of this memo is to provide an outline for the investigator on the manufacturing steps that take place at the Alexza site and to provide an overview of the device components that are manufactured elsewhere. In particular, the critical heat package component will be described and the potential risks associated with a lack of rigorous control over its manufacture will be outlined.

The drug product is composed of three main components (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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/s/

DAVID J CLAFFEY
05/21/2010

RAMESH K SOOD
05/21/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 22549
Brand Name	Staccato Loxapine for Inhalation
Generic Name	Loxapine
Sponsor	Alexza Pharmaceuticals, Inc
Indication	Acute Treatment of Agitation
Dosage Form	Inhalation - hand-held drug-device
Drug Class	dopamine-blocking agent
Therapeutic Dosing Regimen	10 mg
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	10 mg
Submission Number and Date	12/11/2009
Review Division	Division of Psychiatry Products

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of *Staccato*® Loxapine (10 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between *Staccato*® Loxapine (10 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, double-blinded, 3-period crossover study, 48 healthy subjects were randomized and received at least 1 dose of study medication of *Staccato*® Loxapine (10 mg), placebo, and a single oral dose of moxifloxacin 400 mg. Of the 48 randomized subjects, 46 completed the study. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for *Staccato*® Loxapine (10 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
<i>Staccato</i> Loxapine 10 mg	1	5.7	(3.0, 8.4)
Moxifloxacin 400 mg*	3	9.6	(6.7, 12.5)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 5.6 ms.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL:



2.2 QT-IRT RECOMMENDATION

We have the following recommendations which are suggestions only. We defer all final labeling decisions to the review division.

The effect of *Staccato*® Loxapine on QTc prolongation was evaluated in a randomized, double-blinded, positive-(moxifloxacin 400 mg) and placebo-controlled parallel study in healthy subjects. A total of 48 healthy subjects were administered *Staccato*® Loxapine (10 mg). In a study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Staccato® Loxapine for Inhalation (*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. Loxapine binds with high affinity to dopamine D₂ receptors and acts as an antagonist at this receptor, as well as binding with high affinity at serotonin 5-HT_{2A} receptors.

3.2 MARKET APPROVAL STATUS

Staccato Loxapine represents a new dosage form for loxapine, an antipsychotic that has been available in the United States (US) since 1975.

3.3 PRECLINICAL INFORMATION

From the IB (Oct 21, 2008)

Adding loxapine to isolated rabbit hearts (Langendorff preparation) resulted in decreased amplitude of heart movements at doses of 0.1 to 2.5 mg/heart. Coronary flow was affected only marginally by 0.1 or 0.5 mg of loxapine, but was decreased by 69% after administration of 2.5 mg of loxapine per heart. In isolated and perfused guinea pig atria, loxapine (0.05 mg/mL) decreased heart rate by 33% and contractile tension by 31%, with complete arrest after 12 minutes of exposure, with milder effects on heart rate and contractile tension at lower doses. In isolated auricular vessels of rabbits, there was a 51% increase in perfusion volume following 100 µg of loxapine per auricular vessel, although decreases were minor after doses of 1 and 10 µg.

“To explore the potential interaction of loxapine with hERG channels, Alexza conducted a non-GLP in vitro study to evaluate the effects of loxapine on hERG current expressed in stably transfected human embryonic kidney (HEK-293) cells. Loxapine dose-dependently blocked the hERG current with an IC₅₀ value of 1.8 µM (or 590 ng/mL unbound).

“Effects of IV administration of loxapine on cardiovascular function have been evaluated in cats and in dogs. Loxapine administration produced dose-dependent hypotension in 2 studies in anesthetized cats, with no significant effects on heart rate, PR interval, or ECG patterns in the 1 study in which these parameters were monitored.

“In addition to these cat studies, the NDA sponsor conducted multiple cardiovascular studies with IV loxapine in anesthetized dogs. At the dose range studied (0.5-4 mg/kg), the effects of loxapine trended towards reduction of blood pressure, reduced arterial blood flow, increased cardiac contractility, and increased cardiac output. Heart rate was not affected by loxapine treatment and there were no consistent changes in ECG parameters. However, when the dose of loxapine was increased to 7.5 mg/kg (cumulative IV dose), 1 dog developed markedly elevated T-waves and expired in cardiac arrest.

“In conscious telemetered beagle dogs. Rapid IV bolus (5 seconds) of loxapine (0.15, 0.5 or 1.5 mg/kg) was used to mimic inhalation administration of the drug, (a separate study showed that the pharmacokinetics profile of inhalation exposure to loxapine in dogs was similar to that by IV bolus exposure, supporting this approach). No changes in heart rate or mean arterial blood pressure were observed following vehicle administration or following the lowest loxapine dose tested (0.15 mg/kg). Following the intermediate loxapine dose (0.5 mg/kg), mild increases in heart rate were recorded but no changes in mean arterial blood pressure were noted. After the high dose of 1.5 mg/kg loxapine, mean arterial blood pressure decreased transiently 20 seconds post-dose (by approximately 22%). This decrease in mean arterial blood pressure was followed by an immediate increase, which lasted until approximately 6 minutes post-dose. No changes in ECG intervals attributable to loxapine or vehicle administration were observed at any dose tested. Loxapine administration did not lead to QT or QTc prolongation.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From module 2, clinical overview

To support the proposed indication for *Staccato* Loxapine, its safety has been studied in healthy subjects, in agitated patients with schizophrenia or bipolar disorder, in non-agitated subjects on stable antipsychotic regimens, in subjects with asthma, and in subjects with COPD. The safety database comprises a total of 1653 subjects (Overall Safety Population) of which 1147 subjects received *Staccato* Loxapine and 578 subjects received *Staccato* Placebo. (Included in these numbers are 72 subjects who received both *Staccato* Loxapine and *Staccato* Placebo in crossover studies.) The dose levels of *Staccato* Loxapine have ranged from 0.625 mg in an early Phase 1 study up to 10 mg, the recommended dose for treatment of agitation in schizophrenia and bipolar disorder. Total daily doses have ranged from 0.625 to 30 mg.

Table 2: *Staccato* Loxapine Adverse Events with an Incidence of at least 2% and Greater than Placebo (Controlled Studies in Agitated Patient Population)

MedDRA Preferred Term n (%)	Placebo (N=263)	<i>Staccato</i> Loxapine 5 mg (N=265)	<i>Staccato</i> Loxapine 10 mg (N=259)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)
p-value		0.0102	0.0003
Sedation/Somnolence	25 (9.5%)	32 (12.1%)	31 (12.0%)
p-value		0.4005	0.3978
Sedation	20 (7.6%)	28 (10.6%)	27 (10.4%)
p-value		0.2894	0.2866
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)
p-value		1.0000	0.7245
Throat Irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)
p-value		1.0000	0.0364

Note: p-values are from the Fisher's exact test.

Source: m2.7.4.2.1.1.1, Table 15

“Among the most commonly reported cardiovascular side effects are hypotension, tachycardia, and hypertension; orthostatic effects have also been reported. Other reported cardiovascular side effects include lightheadedness, syncope, and palpitations. Electrocardiogram (ECG) changes have been reported in a few cases. Although loxapine blocks the hERG channel, it does so at a relatively high concentration, indicating a relatively low risk for QT prolongation with therapeutic doses; QT prolongation has been reported with overdose.

“Alexza’s review identified 15 deaths in the loxapine literature, with slightly more than half attributed to suicide and/or overdose (n=8). Other cited causes of death were myocardial infarction/heart disease (n=2), neuroleptic malignant syndrome (n=1), head injury during altercation (n=1), and opioid-induced neurotoxicity (n=1); no cause was identified for 2 of the 15 deaths.”

Reviewer’s comments: No seizure, sudden cardiac death or ventricular arrhythmias were reported. QT prolongation was reported with overdose.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Loxapine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 73248. The sponsor submitted the study report AMDC-004-107 for the study drug *Staccato*® Loxapine, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Thorough QT/QTc Study of *Staccato*® Loxapine for Inhalation in Healthy Volunteers

4.2.2 Protocol Number

AMDC-004-107

4.2.3 Study Dates

First Subject Randomized: 23 April 2009

End of Protocol-Mandated AE Reporting Period: 06 July 2009

4.2.4 Objectives

Primary Objective: To assess the maximum effect of *Staccato* Loxapine on cardiac repolarization (QTc interval duration) at the anticipated maximum clinical dose compared to placebo in healthy volunteers.

Secondary Objective: To assess the QTc versus loxapine concentration relationship following treatment with *Staccato* Loxapine in healthy volunteers.

4.2.5 Study Description

4.2.5.1 Design

This was a double-blind, double-dummy, active- and placebo-controlled, 3-period crossover study. Subjects received 3 treatments, separated by a minimum 3-day washout period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were overencapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Treatment	Oral	Inhalant
A	placebo	<i>Staccato</i> Loxapine 10 mg
B	placebo	<i>Staccato</i> Placebo
C	moxifloxacin 400 mg	<i>Staccato</i> Placebo

Female and male subjects in approximately equal numbers will be randomly assigned (1:1:1:1:1:1) to receive the 3 treatments according to 1 of 6 sequences:

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	C	A
4	B	A	C
5	C	A	B
6	C	B	A

4.2.6.2 Sponsor's Justification for Doses

“The *Staccato* Loxapine dose chosen for use in this study was 10 mg. This is the maximum dose that has been studied in healthy volunteers and is the anticipated maximum dose for the treatment of agitation in patients with schizophrenia and bipolar disorder. *Staccato* Loxapine has been evaluated in 2 studies in healthy volunteers who received single doses up to 10 mg (Studies [AMDC-004-101](#) and [AMDC-004-103](#)). Results from these studies indicate that 10 mg is the maximum dose suitable for single-dose administration to healthy volunteers based on the common occurrence of central nervous system effects (eg, sedation) and the uncommon occurrence of cardiovascular effects (eg, hypotension).”

Reviewer's Comment: The dose selection seems to be acceptable.

4.2.6.3 Instructions with Regard to Meals

“To minimize interference with study assessments, each subject received breakfast after the morning predose assessment, but before the oral dosing. When subsequent assessments and meals were scheduled at approximately the same time, assessments were always performed first within 10 minutes of the nominal time point and in the following sequence: ECG, vital signs, blood sampling, serve meal. Decaffeinated beverages and water were available upon request throughout the visit.”

Reviewer's Comment: Acceptable. No effect of meals on the exposure to loxapine is expected due to pulmonary route of administration.

4.2.6.4 ECG and PK Assessments

Time, rel. to Oral Drug Admin	Pre-dose	0	1 h	1.5 h	2 h	121 min	122 min	125 min	129 min	135 min	2.5 h	3 h	5 h	8 h	12 h	24 h
Time, rel. to Inhaled Drug Admin	-	-2 h	-1 h	-30 min	0	1 min	2 min	5 min	9 min	15 min	30 min	1h	3 h	6 h	10 h	22 h
Vital signs ^a	X			X	X					X	X	X	X	X	X	X
Routine laboratory tests ^b	X															X
Oral drug administration		X														
Inhaled drug administration					X											
PK sampling (venous)	X			X		X	X	X	X	X	X	X	X	X	X	X
Safety ECGs	X									X			X			
ECG QT sampling ^c	X		X	X		X	X	X	X	X	X	X	X	X	X	X
AE evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PredischARGE assessment																X

AE=adverse event, ECG=electrocardiogram, PK=pharmacokinetic

a. Vital signs included blood pressure, heart rate, respiration rate, and temperature.

b. Routine laboratory tests included chemistry, hematology, and urinalysis parameters; pre-dose sample collection took place at admission and discharge

c. Holter monitoring was started about 45 minutes before dosing and continued throughout the post-dosing period.

Source: Appendix 12.1.1, Study Protocol [Appendix 1](#).

Source: The sponsor's report "Thorough QT/QTc Study of Staccato® Loxapine for Inhalation in Healthy Volunteers" page 32.

Reviewer's Comment: The sampling times are acceptable. PK and ECGs measurements were collected frequently enough to monitor the effects of loxapine. The sponsor has collected ample ECG measurements before, around, and after the T_{max}.

4.2.6.5 Baseline

Baseline assessments were collected on the baseline day only at period 1 in the 3-period crossover study.

4.2.7 ECG Collection

A single clinical center highly experienced in conducting "thorough" QT/QTc studies was used for study conduct. A blinded core laboratory, employing a manual methodology and single cardiologist, was used to read the ECGs. ECG readings were carried out in a digital, onscreen environment with annotation of interval onset and offset points. The cardiologist was blinded to period, sequence, and treatment.

All ECGs were interpreted centrally by US board-certified cardiologists at (b) (4) in a blinded fashion without knowledge of therapy or sequence including the active control. All the electrocardiograms whether transmitted directly by modem from the ELI-150 digital electrocardiograph (screening) or those that are transmitted over a secured internet interface and subsequently extracted from the H-12 Plus ambulatory electrocardiograph recorder (study electrocardiograms) were analyzed manually utilizing the same validated digital techniques of E-Scribe™ and the Veritas™ algorithm (Mortara Instruments, Milwaukee, WI).

The QT intervals are measured using a high-resolution manual on-screen caliper method in compliance with the suggested standards set forth in The FDA Guidance for Industry E-14 Clinical Evaluation of QT/QTc Interval Prolongation, October 2005. The initial measurements are performed by certified Cardiovascular Credentialing International (CCI) cardiovascular technicians using the median representative beat method, and all measurements are confirmed or re-adjusted by the cardiologist. The default primary lead for these measurements is Lead II. The RR interval is the average of the beats within the 10 second acquisition. Where artifact, wandering, lead reversal, or insufficient T wave amplitude prohibit measurement in Lead II, lead V5 or global beat fine tuning may be required and will be reported in the final Cardiac Safety Report. T-U wave morphologic changes are reported in a detailed manner so that they can be characterized into 4 categories ranging from a normal U wave variant to an early after depolarization. The final Cardiac Safety Report includes the number and percentage of tracings fall into each of the 4 categories with an assessment of severity.

4.2.8 Sponsor's Results

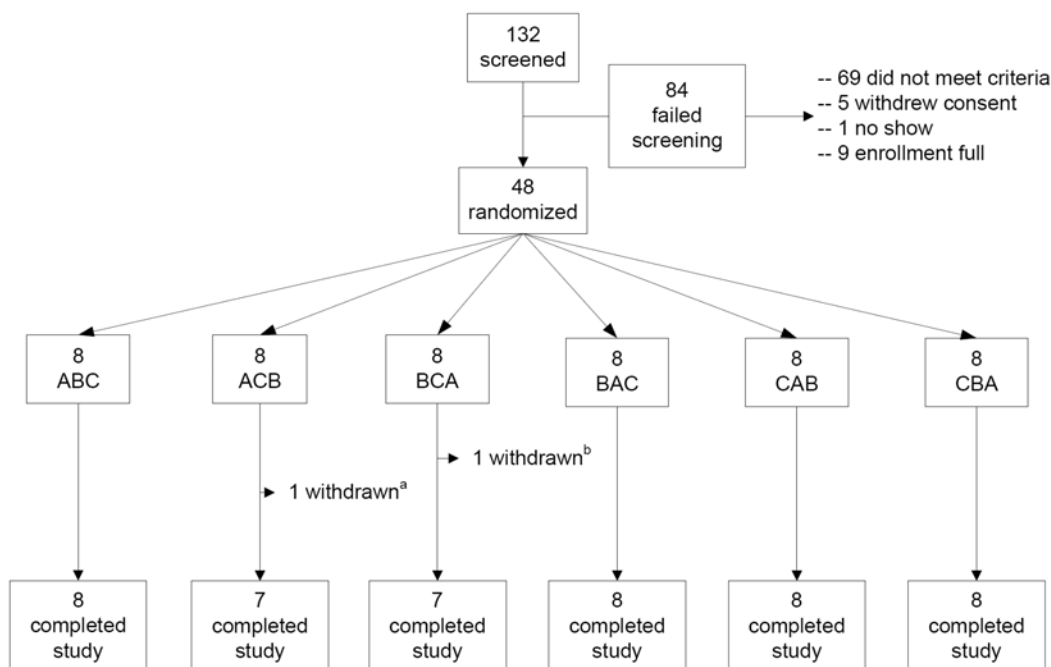
4.2.8.1 Study Subjects

Male or female (n=132) between the ages of 18 to 65 years, body mass index ≥ 21 and ≤ 30 were screened. Forty eight subjects (36.4%) were randomized and received at least 1 dose of study medication, and 46 completed the study.

The two subjects who discontinued prematurely are briefly described below:

Subject 01-011 (female, age 22) reported ingestion of alcohol before her third treatment (B) and was withdrawn by the investigator.

Subject 01-045 (male, age 28) received 1 treatment (B), but did not appear for Visit 3 at the CRU as scheduled and was consequently designated as lost to follow-up.



Treatment: A = *Staccato* Loxapine 10 mg, B = Placebo, C = Oral Moxifloxacin 400 mg

a. Withdrawn after Treatments A and C

b. Withdrawn after Treatment B

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary outcome was the difference from the pre-dose baseline at each time point in the individual subject-corrected QT interval, QTcI. The primary endpoint was based on least squares mean (LSmean) corrected for baseline QTcI, Sequence, Period, Time, Treatment group and the interaction of Time and Treatment group according to the repeated measures model.

Table 3 shows that, *Staccato* Loxapine at a dose of 10 mg did not increase QTc intervals, as demonstrated by the upper bound of the placebo-subtracted change of QTcI ($\Delta\Delta\text{QTcI}$) being less than 10 ms at all post-dose times. The maximum $\Delta\Delta\text{QTcI}$ occurred at 1 hour post-dose (LS mean 5.42 ms, upper confidence bound 7.75 ms).

Table 3: Point Estimates and Upper Bounds from Sponsor's Analyses on $\Delta\Delta\text{QTcI}$ for *Staccato* Loxapine 10 mg

Time Post-Dose	$\Delta\Delta\text{QTcI}$ <i>Staccato</i> Loxapine 10 mg	Upper 95% Confidence Bound
1 min	0.031	2.352
2 min	-0.119	2.203
5 min	1.817	4.139
9 min	3.613	5.934
15 min	2.156	4.477
30 min	4.499	6.820
1 hour	5.418	7.753
3 hour	4.560	6.895
6 hour	1.438	3.773
10 hour	1.667	4.014
22 hour	-1.404	0.917

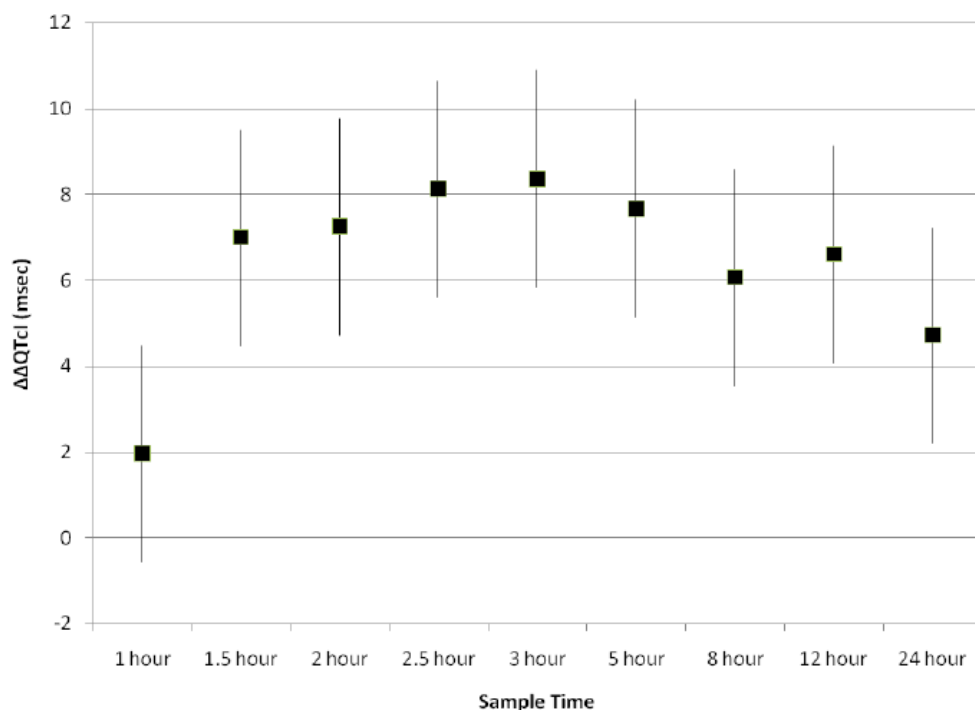
Source: Table 12, Clinical Study Report [Alexza Study AMDC-004-107], Page 56

Reviewer's Comment: the statistical reviewer performed an independent analysis, and the overall conclusions are the same as the sponsors.

4.2.8.2.2 Assay Sensitivity

Assay sensitivity was demonstrated by the lower two-sided 90% confidence bounds of $\Delta\Delta\text{QTcI}$ being greater than 5 ms at 2 (2.5 and 3 hours) of the 4 times post-dose, chosen a priori (1.5, 2, 2.5 and 3 hours), and the expected time course of the moxifloxacin response. The results were not adjusted for multiple testing.

Figure 1: Moxifloxacin QTcI, LS mean Differences from Placebo in Change from Baseline and 90% CI



CI is represented by two-sided 90% upper and lower confidence bounds

Source: Figure 5, Clinical Study Report [Alexza Study AMDC-004-107], Page 59

Reviewer's Comments: To establish assay sensitivity, the results should be adjusted for multiple testing. Please refer to the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

The following categorical outliers for each QT correction factor (I, F, and B) were identified:

- Post-dose QTc > 450 ms
One subject on placebo had a single QTcI > 450 ms and one subject on *Staccato* Loxapine 10 mg had two QTcI intervals > 450 ms. Similar results were seen for QTcF.
Four subjects on *Staccato* Placebo had one or more QTcB intervals > 450 ms and three subjects on *Staccato* Loxapine 10 mg had one or more QTcB intervals > 450 ms
- Post-dose QTc > 480 ms
No subject had any QTc > 480 ms at any time.
- Post-dose QTc > 500 ms
No subject had any QTc > 500 ms at any time.
- Increase in QTc from the pre-dose baseline > 30 ms
One subject on *Staccato* placebo and one subject on *Staccato* Loxapine 10 mg each had a single increase from baseline in QTcI > 30 ms. Similar results were seen for QTcF.

Six subjects who received *Staccato* Placebo and six subjects who received *Staccato* Loxapine 10 mg each had one or more increases from baseline in QTcB > 30 ms.

Three subjects had an increase in QTcB > 30 ms on both placebo and *Staccato* Loxapine 10 mg.

- Increase in QTc from the pre-dose baseline > 60 ms

No subject had an increase from baseline in any QTc > 60 ms.

4.2.8.3 Safety Analysis

With the exception of one AE of unknown severity post placebo treatment (Subject 01-006), all AEs reported in this study were judged as mild or moderate. The percentage of subjects with any AE was similar in the moxifloxacin and placebo groups, but the percentage with treatment-related AEs was higher in the *Staccato* Loxapine group. The most common AEs associated with *Staccato* Loxapine treatment were somnolence, dizziness, dysgeusia, and cough.

Table 4: Overview of Adverse Events (Safety Population)

Percent of Subjects with:	<i>Staccato</i> Loxapine 10 mg (N=47)	Placebo ^a (N=47)	Oral Moxifloxacin 400 mg (N=47)
Any AE	80.9%	40.4%	19.1%
Treatment-related AEs	78.7%	27.7%	17.0%
Severe AEs	0.0%	0.0%	0.0%
Treatment-related severe AEs	0.0%	0.0%	0.0%
AEs leading to discontinuation	0.0%	0.0%	0.0%
Any SAE	0.0%	0.0%	0.0%
Treatment-related SAEs	—	—	—
SAEs leading to discontinuation	—	—	—
Death	0.0%	0.0%	0.0%

a. Placebo includes exposure to oral placebo prior to inhalation exposure and post inhalation exposure when both oral and inhalation were placebo

Note: All AEs presented in this study report were judged to be treatment emergent.

Source: Section 11.1, [Tables 3.2, 3.3, 3.4, 3.5, 3.6](#); Appendix 12.2, [Listings 1.2, 3.1, 3.2](#)

Source: CSR, table 17

The greatest frequency of AEs (80.9%) was observed in subjects receiving *Staccato* Loxapine compared with placebo (40.4%) and moxifloxacin (19.1%). Of the AEs that occurred most frequently after *Staccato* Loxapine treatment (61.7% somnolence, 36.2% dizziness, 19.1% dysgeusia, and 14.9% cough), somnolence and dizziness are known effects of loxapine administered by other routes, and dysgeusia and cough commonly occur with inhaled products. Somnolence, dizziness, dysgeusia, and cough were also reported by subjects treated with moxifloxacin and placebo; however, the incidence of these AEs was lower, with dizziness, dysgeusia, and cough reported by ≤4.3% of subjects and somnolence reported by 14.9% of subjects after placebo treatment.

All episodes of dysgeusia resolved, most within 5 minutes; 3 resolved after subjects drank water. All incidents of dysgeusia were judged as mild. All AEs were designated mild or moderate in nature. No deaths occurred in this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Summary statistics of the pharmacokinetics of Loxapine and 7-OH-loxapine are provided in Table 5.

Table 5: Summary Statistics for Loxapine and 7-OH-Loxapine Pharmacokinetic Parameter Estimates.

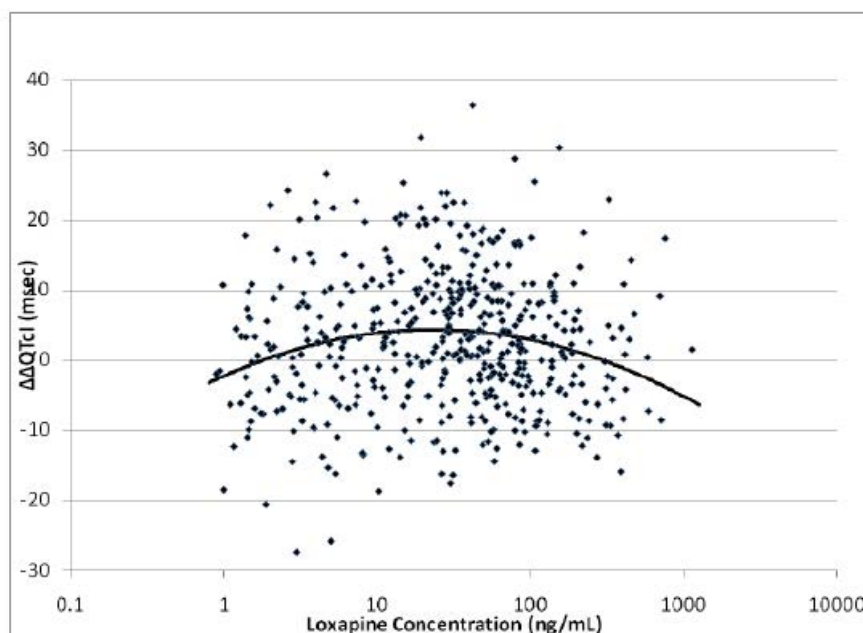
Parameter	Loxapine (N=47)	7-OH-Loxapine (N=47)
AUC _{inf} (ng*h/mL), mean ± SD	202.4 ± 47.2	30.4 ± 8.1
AUC _{last} (ng*h/mL), mean ± SD	182.8 ± 42.4	21.4 ± 5.7
AUC _{0-2hr} (ng*h/mL), mean ± SD	75.2 ± 18.4	2.0 ± 0.8
C _{max} (ng/mL), mean ± SD	312.2 ± 225.1	1.6 ± 0.5
T _{max} (min), median (minimum, maximum)	0.98 (0.75, 4.95)	179.92 (59.85, 359.93)
k _e (L/h), mean ± SD	0.095 ± 0.032	0.060 ± 0.012
T _{1/2} (h), mean ± SD	7.92 ± 1.98	12.00 ± 2.20
CL/F (L/h), mean ± SD	51.9 ± 11.1	—

Source: The sponsor's report "Thorough QT/QTc Study of *Staccato*® Loxapine for Inhalation in Healthy Volunteers" page 61.

4.2.8.4.2 Exposure-Response Analysis

The relationship between ΔQTcI interval and corresponding loxapine concentration was shown in Figure 2. The relationship between delta QTcI and loxapine concentration was shown as nonlinear, indicating that there was no positive concentration-response relationship. The median observed loxapine concentration (32.1 ng/mL) was associated with a mean of 4.25 ms and upper confidence bound of 5.62 ms with a slope of 0.11 ms/(μgEq/mL) (90% CI = [-0.11; 0.32]).

Figure 2: Scatter Plot of delta QTcI versus PK Concentrations with Regression Line Overlaid – Pharmacokinetic/ECG Pharmacodynamic Population



Source: The sponsor's report "Thorough QT/QTc Study of *Staccato*® Loxapine for Inhalation in Healthy Volunteers" page 60.

Table 6: $\Delta\Delta\text{QTcI}$ at Loxapine Quartile-Concentrations, Change from Baseline

Percentile	Loxapine [ng/mL]	Diff	SEM	5% CI	90% CI
Minimum	0.89	-2.804	1.466	-5.220	-0.389
25th	9.20	3.750	0.660	2.658	4.841
Median	32.1	4.238	0.827	2.859	5.617
75th	78.4	3.297	1.021	1.584	5.010
Maximum	1120	-5.874	2.978	-10.804	-0.944

Placebo-subtracted changes from baseline of QTcI (ms) from regression versus loxapine concentration (ng/mL) at quartile loxapine concentrations

Source: The sponsor's report "Thorough QT/QTc Study of *Staccato*® Loxapine for Inhalation in Healthy Volunteers" page 61.

Reviewer's Comment: We performed an independent analysis using linear mixed effect model. The overall conclusions are the same as the sponsors. Our analysis is presented in section 5.2.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 7, it appears that both QTcF and QTcI are similar.

Table 7: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P value
<i>Staccato</i> Loxapine 10 mg	0.00952	0.02351	0.00025
Moxifloxacin 400 mg	0.01944	0.02377	0.37869
Placebo	0.00702	0.00592	0.83345
Overall	0.01597	0.01868	0.24061

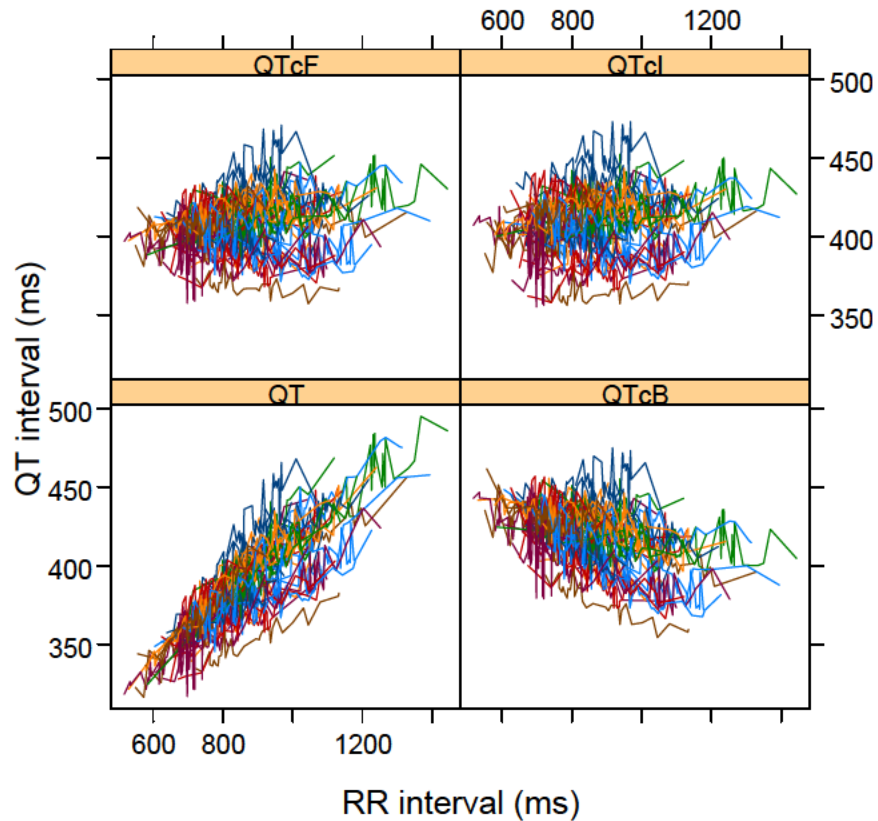
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it also appears that both QTcF and QTcI are similar. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
<i>Staccato</i> Loxapine 10 mg	47	0.0015	47	0.0022
Moxifloxacin 400 mg	47	0.0036	47	0.0045
Placebo	46	0.0021	46	0.0022
All	48	0.0014	48	0.0015

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for *Staccato* Loxapine

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The analysis included data from placebo and *Staccato* Loxapine groups. The model includes TREATMENT, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for *Staccato* Loxapine (10 mg)

	Placebo	Staccato Loxapine 10 mg		
	Δ QTcI	Δ QTcI	$\Delta\Delta$ QTcI	
Time	LS Mean	LS Mean	Diff LS Mean	90% CI
1 min	-8.3	-8.1	0.3	(-2.0, 2.5)
2 min	-6.1	-6.1	0.0	(-1.8, 1.9)
5 min	-5.7	-3.5	2.2	(0.2, 4.3)
9 min	-6.8	-2.7	4.1	(2.3, 5.9)
15 min	-4.3	-1.8	2.5	(0.3, 4.7)
30 min	-6.6	-1.7	4.8	(2.1, 7.6)
1 hour	-4.2	1.6	5.7	(3.0, 8.4)
3 hour	5.3	10.4	5.1	(2.5, 7.8)
6 hour	-4.0	-2.2	1.8	(-0.6, 4.2)
10 hour	-5.2	-3.5	1.8	(-1.1, 4.6)
22 hour	-2.2	-3.1	-0.9	(-3.2, 1.4)

The largest upper bound of the 2-sided 90% CI for the mean difference between *Staccato* Loxapine 10 mg and placebo was 8.4. The reviewer also examined QTcF intervals and the results are consistent with those reported here for QTcI.

5.2.1.2 Assay Sensitivity Analysis

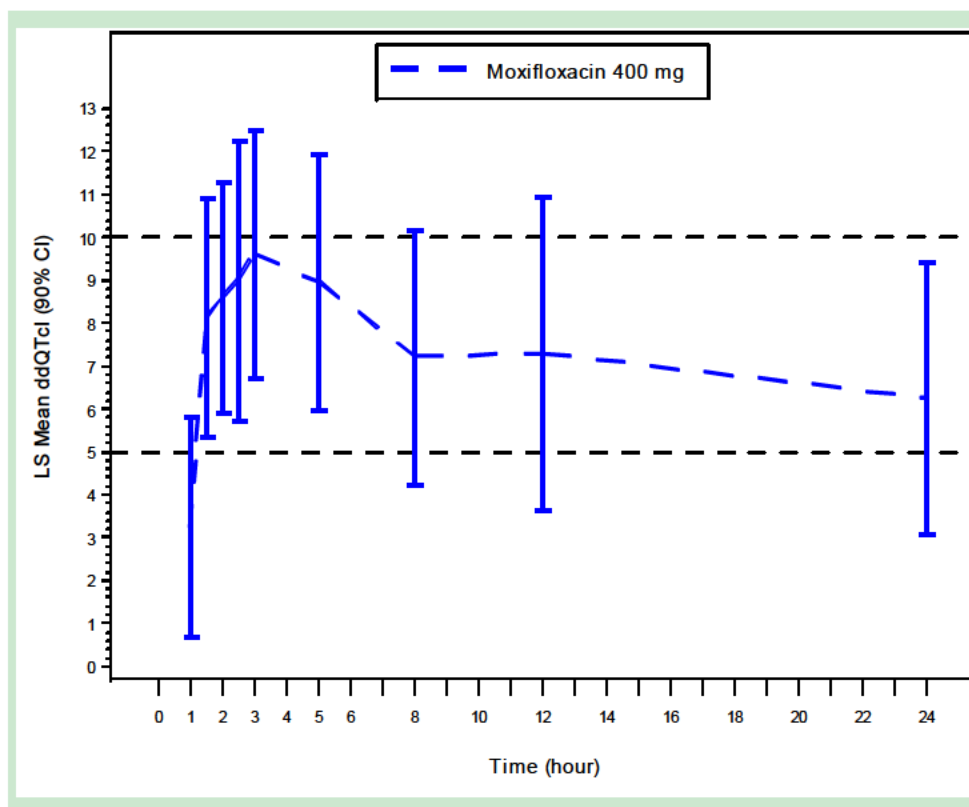
The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The analysis included data from placebo and moxifloxacin groups. The results are presented in Table 10. The largest unadjusted 90% lower confidence interval is 6.7. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval of the 4 times post-dose, is 5.6 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study. The time profile of $\Delta\Delta$ QTcI for moxifloxacin is displayed in Figure 4.

Table 10: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

	Placebo	Moxifloxacin 400 mg			
	Δ QTcI	Δ QTcI	$\Delta\Delta$ QTcI		
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	Adjusted* 90% CI
1	-7.8	-4.6	3.2	(0.7, 5.8)	(-0.2, 6.7)
1.5	-10.5	-2.4	8.1	(5.3, 10.9)	(4.3, 11.9)
2	-14.6	-6.0	8.6	(5.9, 11.3)	(4.9, 12.3)
2.5	-12.3	-3.3	9.0	(5.7, 12.3)	(4.5, 13.5)
3	-10.0	-0.4	9.6	(6.7, 12.5)	(5.6, 13.6)
5	-0.3	8.6	8.9	(6.0, 11.9)	(4.9, 13.0)
8	-9.9	-2.7	7.2	(4.2, 10.2)	(3.1, 11.3)
12	-10.8	-3.5	7.3	(3.6, 10.9)	(2.2, 12.3)
24	-8.1	-1.8	6.2	(3.1, 9.4)	(1.9, 10.6)

- Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Figure 4: Mean and 90% CI for $\Delta\Delta$ QTcI Timecourse for Moxifloxacin



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.3 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 11: Categorical Analysis for QTcI

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Baseline	48	140	47 (97.9%)	139 (99.3%)	1 (2.1%)	1 (0.7%)
Placebo	46	502	45 (97.8%)	501 (99.8%)	1 (2.2%)	1 (0.2%)
Moxifloxacin	47	512	46 (97.9%)	501 (97.9%)	1 (2.1%)	11 (2.1%)
<i>Staccato</i> Loxapine	47	516	46 (97.9%)	514 (99.6%)	1 (2.1%)	2 (0.4%)

Table 12 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of $\Delta QTCI$

	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	46	502	45 (97.8%)	501 (99.8%)	1 (2.2%)	1 (0.2%)
Moxifloxacin	47	512	45 (95.7%)	510 (99.6%)	2 (4.3%)	2 (0.4%)
<i>Staccato</i> Loxapine	47	516	46 (97.9%)	515 (99.8%)	1 (2.1%)	1 (0.2%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper limits of 90% CI for the PR mean differences between *Staccato* Loxapine and placebo is 3.6 ms.

There was only one subject who experienced one PR interval greater than 200 ms in *Staccato* Loxapine 10-mg group.

Table 13: Analysis Results of ΔPR and $\Delta\Delta PR$ for *Staccato* Loxapine

	Placebo	Staccato Loxapine 10 mg		
	ΔPR	ΔPR	$\Delta\Delta PR$	
Time	LS Mean	LS Mean	Diff LS Mean	90% CI
1 min	-4.4	-6.0	-1.6	(-3.7, 0.5)
2 min	-4.4	-5.5	-1.2	(-2.9, 0.6)
5 min	-3.8	-5.2	-1.4	(-3.2, 0.4)
9 min	-2.9	-3.4	-0.6	(-2.7, 1.5)
15 min	-3.2	-2.1	1.1	(-1.1, 3.3)
30 min	-2.5	-1.3	1.2	(-1.2, 3.6)
1 hour	-1.5	-3.9	-2.5	(-5.0, 0.1)
3 hour	-0.5	-0.5	-0.1	(-2.3, 2.2)
6 hour	-5.4	-5.9	-0.5	(-2.5, 1.5)
10 hour	-4.1	-5.8	-1.7	(-3.7, 0.3)
22 hour	-0.2	-0.3	-0.0	(-2.9, 2.8)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the QRS mean difference between *Staccato* Loxapine and placebo is 7.57 ms.

There was only one subject who experienced 5 QRS intervals greater than 110 ms in *Staccato* Loxapine 10-mg group.

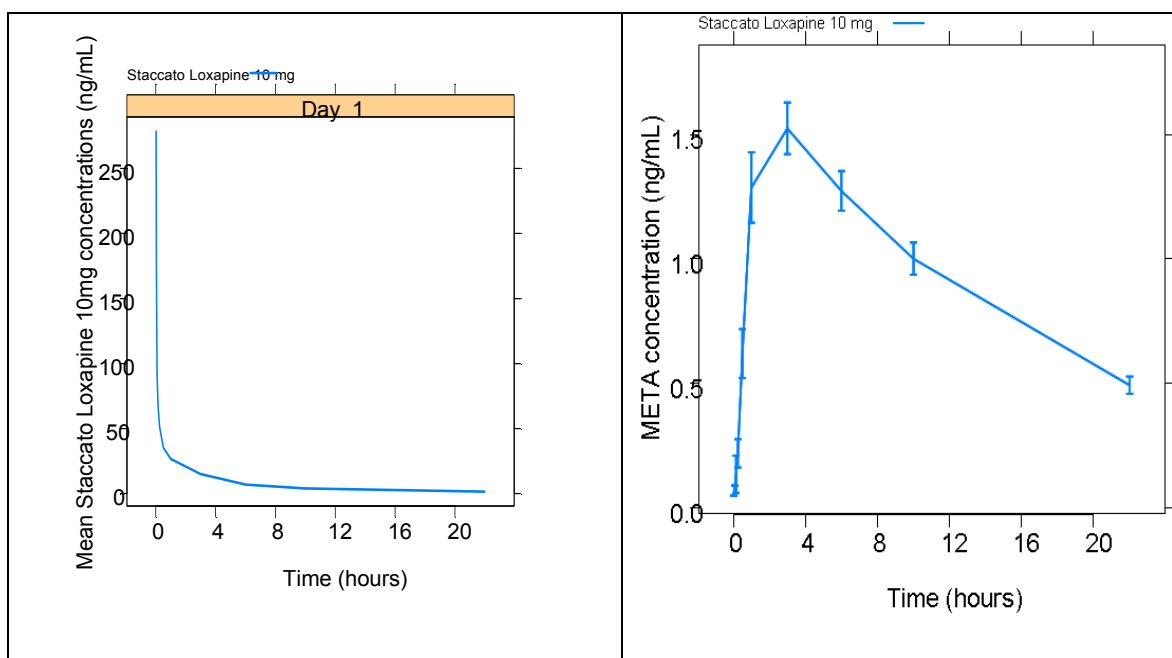
TABLE 14: ANALYSIS RESULTS OF Δ QRS AND $\Delta\Delta$ QRS FOR STACCATO LOXAPINE

	Placebo	Staccato Loxapine 10 mg		
	Δ QRS	Δ QRS	$\Delta\Delta$ QRS	
Time	LS Mean	LS Mean	Diff LS Mean	90% CI
1 min	-1.7	-1.5	0.2	(-0.5, 0.9)
2 min	-1.6	-1.7	-0.0	(-0.8, 0.7)
5 min	-2.0	-1.8	0.2	(-0.5, 0.9)
9 min	-1.8	-1.2	0.7	(-0.1, 1.4)
15 min	-0.9	-0.9	0.0	(-0.8, 0.8)
30 min	-1.5	-0.9	0.6	(-0.2, 1.4)
1 hour	-1.2	-1.4	-0.2	(-1.1, 0.6)
3 hour	-0.3	-0.6	-0.3	(-0.9, 0.4)
6 hour	-0.9	-1.2	-0.3	(-1.2, 0.7)
10 hour	-1.4	-1.5	-0.1	(-1.0, 0.8)
22 hour	-0.8	-0.8	-0.0	(-0.9, 0.8)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

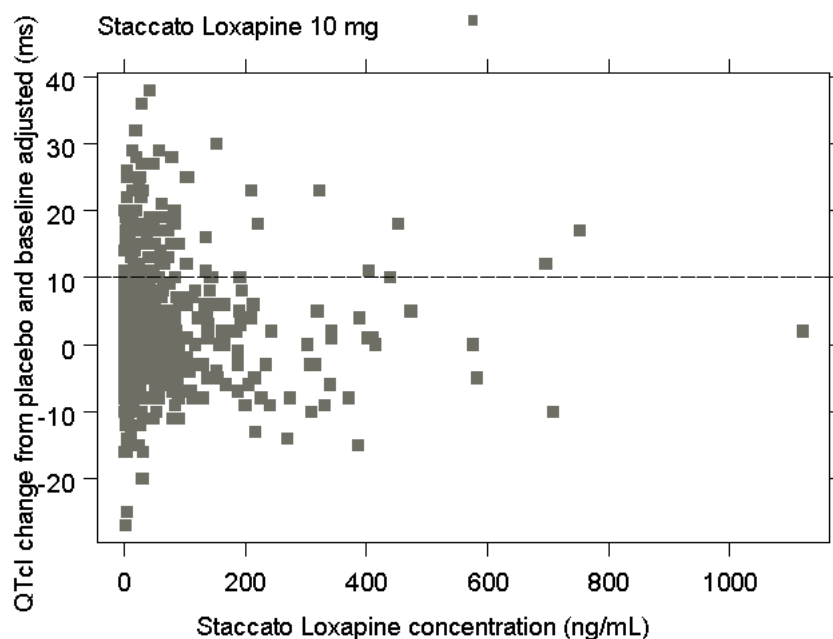
The mean loxapine and 7-OH-Loxapine concentration-time profile is illustrated in Figure 5.

Figure 5: Plasma Loxapine (left) and 7-OH-Loxapine (right) Concentrations at 10mg Dose for 24 Hours.



The relationship between $\Delta\Delta Q_{TcI}$ and *Staccato* Loxapine concentrations is visualized in Figure 2 with no evident exposure-response relationship.

Figure 6: $\Delta\Delta$ QTcI vs. *Staccato* Loxapine Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Staccato Loxapine does not affect PR and QRS duration.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology: *Staccato* Loxapine

Therapeutic dose	10 mg <i>Staccato</i> Loxapine is the maximum proposed clinical dose (see 1.6.1)	
Maximum tolerated dose	A single 10 mg <i>Staccato</i> Loxapine dose is the maximum tolerated dose in healthy volunteers based on the treatment emergent AEs reported in 2 Phase 1 studies (see 1.6.4)	
Principal adverse events	The most common adverse events at the 10 mg dose in the healthy volunteer studies were somnolence (75-100%) and dizziness (31-75%). Hypotension was reported in 1 of 8 subjects in AMDC-004-101 and 3 of 32 in AMDC-004-103. Thus CNS effects (sedation) and cardiovascular effects (hypotension) appear to be dose limiting in healthy volunteers (see 1.6.2).	
Maximum dose tested	Single Dose	10 mg <i>Staccato</i> Loxapine single dose (see 1.5.1)
	Multiple Dose	10 mg Q 4 hr x 3 (30 mg total dose) (see 1.5.6)
Exposures Achieved at Maximum Tested Dose	Single Dose mean (%CV)	C _{max} = 105-359 (69%-103%) ng/mL AUC _{inf} = 141-160 (32%-47%) ng-hr/mL (see 1.6.3)
	Multiple Dose mean (%CV)	C _{max} = 78.4 (81%) ng/mL AUC _{inf} = 315 (46%) ng-hr/mL (see 1.6.3)
Range of linear PK	Excellent dose proportionality has been shown over the entire dosage range studied, 0.625 to 30 mg (see 1.5.7)	
Accumulation at steady state	The accumulation based on the mean PK profiles for the 3 Q 4 hr regimens studied (C _{trough} /C _{peak}) was 9.7% (range 8.4 to 12%) (see 1.5.6)	
Metabolites	The mean ± SD within-subject metabolite-to-parent ratios for the AUC _{last} were: 18.3% ± 10.0% (N=17) for 7-OH-loxapine; 50.2% ± 22.6% (N=9) for 8-OH-loxapine; 9.2% ± 5.6% (N=3) for amoxapine. The activity of the metabolites has not been formally studied. (see 1.5.5)	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability has not been assessed in humans, > 95% in dog study (see 1.4.1)
	T _{max} median [range]	for loxapine = 2 [0.5, 60] min for 7-OH-loxapine 2 [0.75, 6] hr (see 1.5.2)
Distribution	Vd/F or mean (%CV)	Vd/F = 633 (45%) L (see 1.5.3)
	% bound	Protein binding (humans) 96.6% (see 1.4.2)

Note : Each highlight is linked to the supporting section of Protocol AMDC-004-107

Elimination	Route	<ul style="list-style-type: none"> • Metabolism to loxapine N-oxide via flavin-containing monooxygenases (FMOs), and partially via cytochrome P-450 • Renal elimination is of conjugated metabolites (see 1.4.4).
	Terminal T _{1/2} mean (%CV)	<ul style="list-style-type: none"> • for loxapine = 6.19 (27%) hr • for 7-OH-loxapine = 9.55 (37%) hr (see 1.5.4)
	CL/F or CL mean (%CV)	<ul style="list-style-type: none"> • for loxapine = 103 (50%) L/hr (see 1.5.4)
Intrinsic Factors	Age	None detected (see 1.5.8)
	Sex	None detected (see 1.5.8)
	Race	None detected (see 1.5.8)
	Hepatic & Renal Impairment	Loxapine PK has not been evaluated in patients with compromised hepatic or renal function (see 1.5.8)
Extrinsic Factors	Drug interactions	None anticipated due to single dose and pulmonary route of delivery (see 1.5.9)
	Food Effects	No effect anticipated due to pulmonary route (see 1.5.9)
Expected High Clinical Exposure Scenario	Since absorption is rapid and nearly 100%, the worst case high exposure scenario is well represented by the maximum doses studied in Phase 1 (see 1.5.10)	

Note : Each highlight is linked to the supporting section of Protocol AMDC-004-107

6.2 TABLE OF STUDY ASSESSMENTS

Procedures	Screening	Admission Day	Baseline QT Day (Period 1 only)	Treatment Period	Termination (24 hr)	Washout ≥3 days	Repeat for Treatment Periods 2 and 3 (no Baseline Day)
Informed consent	X						
Medical history	X						
Physical examination	X	X			X		
Vital signs (BP, HR, RR, T)	X	X	X	X	X		
Routine clinical lab and U/A	X	X					
Urine drug and alcohol screen	X	X					
Serum Pregnancy test	X	X					
Breathing maneuver training	X	X					
Study-drug administration				X			
PK sampling (venous)				X			
Safety ECG	X ^a			X			
ECG QT sampling			X ^b	X ^b			
Adverse event evaluation			X	X	X		

^a Screening ECG is also transmitted to and read by the ECG Core Lab.

^b Holter monitoring is started about 45 min prior to dose and continued throughout postdosing period.

Time, rel. to Active Control Admin	Pre dose	0	1 hr	1.5 hr	2 hr	121 min	122 min	125 min	129 min	135 min	2.5 hr	3 hr	5 hr	8 hr	12 hr	24 hr
Time, rel. to Study Drug Admin	-	-2 hr	-1 hr	-30 min	0	1 min	2 min	5 min	9 min	15 min	30 min	1 hr	3 hr	6 hr	10 hr	22 hr
Vital signs (BP, P, RR, T)	X			X	X					X	X	X	X	X	X	X
Routine clinical lab; UA	X															X
Active Control administration		X														
Study-drug administration					X											
PK sampling (venous)	X			X		X	X	X	X	X	X	X	X	X	X	X
Safety ECGs	X									X			X			
ECG QT sampling	X ^a		X	X		X	X	X	X	X	X	X	X	X	X	X
AE evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-discharge assessment																X

^a Holter monitoring is started about 45 min prior to dose and continued throughout postdosing period.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

JOANNE ZHANG
04/22/2010

XIANG LING
04/22/2010

JOO YEON LEE
04/22/2010

HAO ZHU
04/22/2010

MONICA L FISZMAN
04/22/2010

NORMAN L STOCKBRIDGE
04/22/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022549 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Loxapine Established/Proper Name: Staccato Loxapine Dosage Form: Inhalation Strengths: 5mg; 10mg		
Applicant: Alexza Pharmaceuticals Agent for Applicant (if applicable): NA		
Date of Application: 12/11/2009 Date of Receipt: 12/11/82009 Date clock started after UN: NA		
PDUFA Goal Date: 10/11/2010	Action Goal Date (if different):	
Filing Date: 02/09/2010	Date of Filing Meeting: 01/21/2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) </div> <div> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> </div>	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 20px;"> <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority </div> <div> <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted </div> </div>	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device </div> </div>	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: </div> <div> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical </div> </div>	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): NA				
List referenced IND Number(s): 073248				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>			✓	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:		✓		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
<p><i>Note:</i> 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</p>	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?		✓		
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		✓		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		✓		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?				
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)				
If yes, # years requested: 3	✓			
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		✓		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance¹?</p> <p>If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	✓			
<p>Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p>		✓		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>			✓	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	✓			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	✓			Not originally in submission but was submitted separately on 2/4/10.
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	✓			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		✓		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		✓		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	✓			Request was submitted separately from the submission.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	✓			
Is the PI submitted in PLR format?	✓			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			OSE notified DDMAC
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			✓	
REMS consulted to OSE/DRISK?			✓	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		✓		Will send to OSE PM
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	✓			

Are annotated specifications submitted for all stock keeping units (SKUs)?			✓	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?			✓	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	✓			CDRH: 12/23/09 DPAP: 12/23/09 DSI: 2/16/10 QT: 1/27/10
<i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 2/27/07	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/22/09	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-21-2010

BLA/NDA/Supp #: 022549

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: Staccato loxapine for inhalation

DOSAGE FORM/STRENGTH: Inhalation device / 5 and 10 mg

APPLICANT: Alexza Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of agitation associated with schizophrenia or bipolar disorder.

BACKGROUND: Alexza Pharmaceuticals Inc. has submitted a New Drug Application to support the marketing approval of Staccato® Loxapine for Inhalation (*Staccato Loxapine*) as a prescription drug product for the indication of *rapid treatment of agitation associated with schizophrenia or bipolar disorder in adults*. *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 (aerosol) for loxapine, an antipsychotic that has been available in the United States (US) since 1975. Oral loxapine is used in the treatment of schizophrenia.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kimberly Updegraff	Y
	CPMS/TL:	Keith Kiedrow	N
Cross-Discipline Team Leader (CDTL)	Robert Levin		Y
Clinical	Reviewer:	Francis Becker	Y
	TL:	Robert Levin	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Andre Jackson	Y
	TL:	Raman Baweja	Y
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Darren Fegley	Y
	TL:	Aisar Atrackhi	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Claffey	Y
	TL:	Tom Oliver	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Judy Park	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer: PM:	LaShawn Griffiths Sandra Griffiths	N Y
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orencia	Y
	TL:	Tejashri Purohit-Sheth	N

Other reviewers	CDRH : Quynh Ni Nguyen	Y
Other attendees	DPAP: Anya Harry DPAP TL: Anthony Durmowicz Stat (Bioequivalence): Don Schuirman	N Y Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues: OCP and CDRH several questions related to the application. Issues resolved during a 1/29/2010 telcon with the sponsor.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Not necessary per Division Director</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	
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<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Per CMC Assessment Lead, CMC PM will request facility inspection.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director 21st Century Review Milestones (see attached) (optional): Yes Comments: Will follow GRMP template	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74 Information request sent with letter.
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

KIMBERLY S UPDEGRAFF
03/04/2010