



Clinical Overview

Adasuve

(*Staccato* loxapine)

Psychopharmacologic Drugs Advisory Committee Meeting
December 12, 2011

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Regulatory History

- **December 11, 2009:** Original New Drug Application (NDA) submitted by the sponsor to FDA
- **October 8, 2010:** Complete Response (CR) action taken, identifying pulmonary toxicity (bronchospasm) as the primary issue
- **December 17, 2010:** Meeting with the sponsor to discuss how the CR issues could be resolved. Risk Evaluation and Mitigation Strategy (REMS) was discussed for mitigating the risk of pulmonary toxicity
- **April 29, 2011:** Meeting with the sponsor to provide conceptual guidance on the components of a REMS
- **August 4, 2011:** Resubmission of NDA with proposed REMS

Adasuve Proposed Indication

Acute treatment of agitation associated with
schizophrenia or bipolar disorder

Frequency of Treatment

- Proposed labeling: 10 mg via inhalation every 2 hours as needed for agitation (max of 3 administrations in 24 hours).
- Proposed labeling: 5 mg may be considered when clinical factors warrant (factors have not been defined).
- Because agitation associated with schizophrenia and bipolar disorder is an acute and intermittent condition, it is anticipated that patients will be treated with Adasuve on an infrequent basis.

Efficacy Trials of Adasuve in Acute Agitation

- Two randomized, double-blind, placebo-controlled, fixed-dose trials investigated 2 dose levels (5 mg and 10 mg) of Adasuve in agitated patients with schizophrenia (Trial 004-301) or bipolar disorder (Trial 004-302).
- Up to 3 doses over 24 hours could be administered as needed for agitation: Dose #2 allowed >2 hours after Dose #1. Dose #3 allowed \geq 4 hours after Dose #2.
- The 5-mg and 10-mg doses were efficacious as measured by the change in Positive and Negative Syndrome Scale-Excited Component (PEC) score from baseline to 2 hours after Dose 1 (vs. placebo).

Key Exclusion Criteria

- Patients with clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema, were excluded from the efficacy trials.

Adverse Reactions in the Efficacy Trials

- In general, the adverse reactions associated with Adasuve were either expected from the known adverse event profile of loxapine or related to the method of loxapine administration (inhalation).
- In the schizophrenia and bipolar trials, the most common adverse reactions were dysgeusia, sedation, fatigue, and throat irritation.

Airway-Related Adverse Events

- In the efficacy trials, 524 patients received Adasuve and 263 received placebo
- Four patients treated with Adasuve developed airway-related adverse reactions compared to none in the placebo group:
 - one (0.2%) patient had bronchospasm requiring rescue w/ albuterol & discontinuation from study
 - two (0.4%) patients had wheezing on the day following drug administration
 - one (0.2%) patient had cough (resolved)

Pulmonary Safety Trials: Airway Adverse Reactions

- In the dedicated pulmonary safety studies, there was significant pulmonary toxicity, particularly in subjects with asthma or COPD.

Can Adasuve be Utilized Safely and Effectively in an Acute Clinical Setting?

Must consider:

1. The known characteristics of acutely agitated patients with schizophrenia and bipolar I disorder
2. The limitations of the trials, i.e., has the intended treatment population been adequately studied and characterized?

Characteristics of Acutely Agitated Patients

- Agitation may be a severe, disruptive complication of schizophrenia and mania.
- Agitation may progress from inner distress (nervousness, restlessness, panic) to an outwardly apparent dysfunctional state (cursing, hostility, difficulty controlling impulses, uncooperative behavior, potential for violence).
- The time course for agitation escalation can be minutes, hours, or days.

Characteristics of Acutely Agitated Patients

- May be uncooperative and severely disorganized
- May be psychotic
- May be unable or unwilling to follow directions for use of the product
- May be unable to give reliable medical history
- May require physical restraint

Characteristics of Intended Population

- There is a high rate of smoking in patients with schizophrenia (88%) and mania (70%).¹
- A higher rate of lung disease would be expected in the intended population when compared to the general population.

Characteristics of Intended Population

- Patients may have undiagnosed pulmonary disease
 - Patients with schizophrenia were less likely than asthma controls to have smoking status noted, and in general were less likely to receive some important general health checks than patients without schizophrenia.¹

¹ Roberts et al.; *Family Practice* 24: 34-40; case-matched retrospective review

Potential Limitations of the Efficacy Trials

Potential concerns about generalizability of results from the study population to the intended patient population:

- Severity of agitation studied
- Very few patients recruited from emergency rooms
- Screening period of up to 2 weeks
- Subjects were screened for ability to perform inhalation maneuver and underwent device training

Sources of Enrollment

Based on follow-up information from 19 investigators from the study sites that enrolled 89% of the patients:

- 59% of study patients presented directly to the study site for treatment.
- 33% of the study patients were enrolled from the community following referral from a medical/mental health professional.
- Much smaller numbers were enrolled from inpatient wards (5.5%) or emergency rooms (2.4%).

Screening Period in the Efficacy Trials

- Screening could span up to 2 weeks in the schizophrenia trial:
 - 82.6% of subjects in the schizophrenia trial were dosed within 2 days of screening
 - 3.5% of subjects in the schizophrenia trial were dosed beyond 7 days from screening
- Screening could span up to 24 hours in the bipolar trial

Device Training

- During the Screening Period, patients were evaluated for their ability to perform the inhalation maneuver required to use the *Staccato* device.
- At baseline, repeat device training began within 1 hour of study drug administration: a plastic model of the device (ie, an empty shell containing no working parts or internal components) was available and could be used.

Advantages of the Controlled Trial Setting

In the controlled setting of clinical trials, it may be easier than in an acute clinical setting to:

- Obtain an accurate history and physical
- Provide instructions for use of the device
- Monitor for the development of respiratory signs and symptoms

Challenges in the Acute Clinical Setting

In an acute clinical setting, it may be more challenging to screen for patients at risk of pulmonary toxicity:

- Patients may not have an established relationship with the healthcare provider.
- Device training may be difficult and less practical.
- Patients may be unable to give reliable medical history.
- Medical records might not be promptly available.
- Healthcare providers may have difficulty performing an adequate physical examination on an acutely agitated, disorganized patient.

Challenges: Monitoring for Bronchospasm

In an acute clinical setting, it may be difficult to monitor patients for early signs and symptoms of bronchospasm.

- Patients may be:
 - Persistently agitated (psychiatric, respiratory distress, reaction to albuterol)
 - Psychotic, paranoid
 - Sedated
- Expertise and availability of appropriate medical staff is required.

Conclusions

There may be unique challenges in using Adasuve safely and effectively in the treatment of acute agitation associated with schizophrenia or bipolar disorder.

Conclusions

If Adasuve is approved, challenges for healthcare providers will include:

- Excluding patients at risk for airway adverse reactions
- Properly training patients in use of the Adasuve device
- Effectively monitoring and treating patients post-dose for respiratory signs and symptoms

Pulmonary Safety of Adasuve (*Staccato* loxapine)

Psychopharmacologic Drugs Advisory Committee Meeting December 12, 2011

Theresa M. Michele, M.D.

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Center for Drug Evaluation and Research

US Food and Drug Administration

Outline

- Pulmonary safety
 - Dedicated pulmonary trials
 - Phase 2 and 3 trials in agitated patients
- Factors increasing risk
- Treatment of bronchospasm
- Conclusions

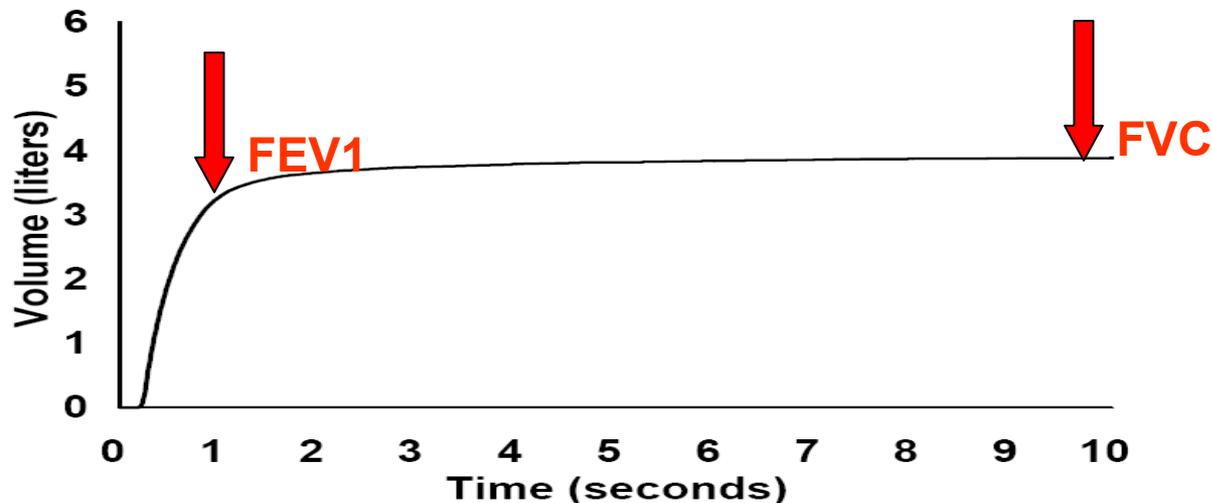
Pulmonary Safety Trials

Study number	N	Population	Dose	Design
004-104	30	Healthy	10 mg x 2 8 hrs apart	Single center Placebo-controlled 2-period crossover
004-105	52	Mild-mod asthma	10 mg x 2 10 hrs apart	Multicenter Placebo controlled Parallel group
004-108	53	Mild-severe COPD	10 mg x 2 10 hrs apart	Multicenter Placebo controlled Parallel group

- **Patients with $\geq 20\%$ drop in FEV1 or respiratory symptoms received albuterol and were not to be re-dosed**

Spirometry Testing

- **FEV1:** Forced expiratory volume in 1 second
- Primary endpoint for many pulmonary trials
- Percent predicted used to stage disease
- Best of 3 acceptable, reproducible efforts
- Normal FEV1 is >80% of forced vital capacity (FVC)



FEV1 Interpretation

- Change of $<8\%$ within measurement variability
- Significant bronchodilator response: improvement of $>12\%$ and 200 mL
- Significant bronchoprovocation response
 - Exercise: $\geq 10\%$
 - Methacholine: $\geq 20\%$
 - Mannitol: $\geq 15\%$

Trial 104: Healthy Volunteers

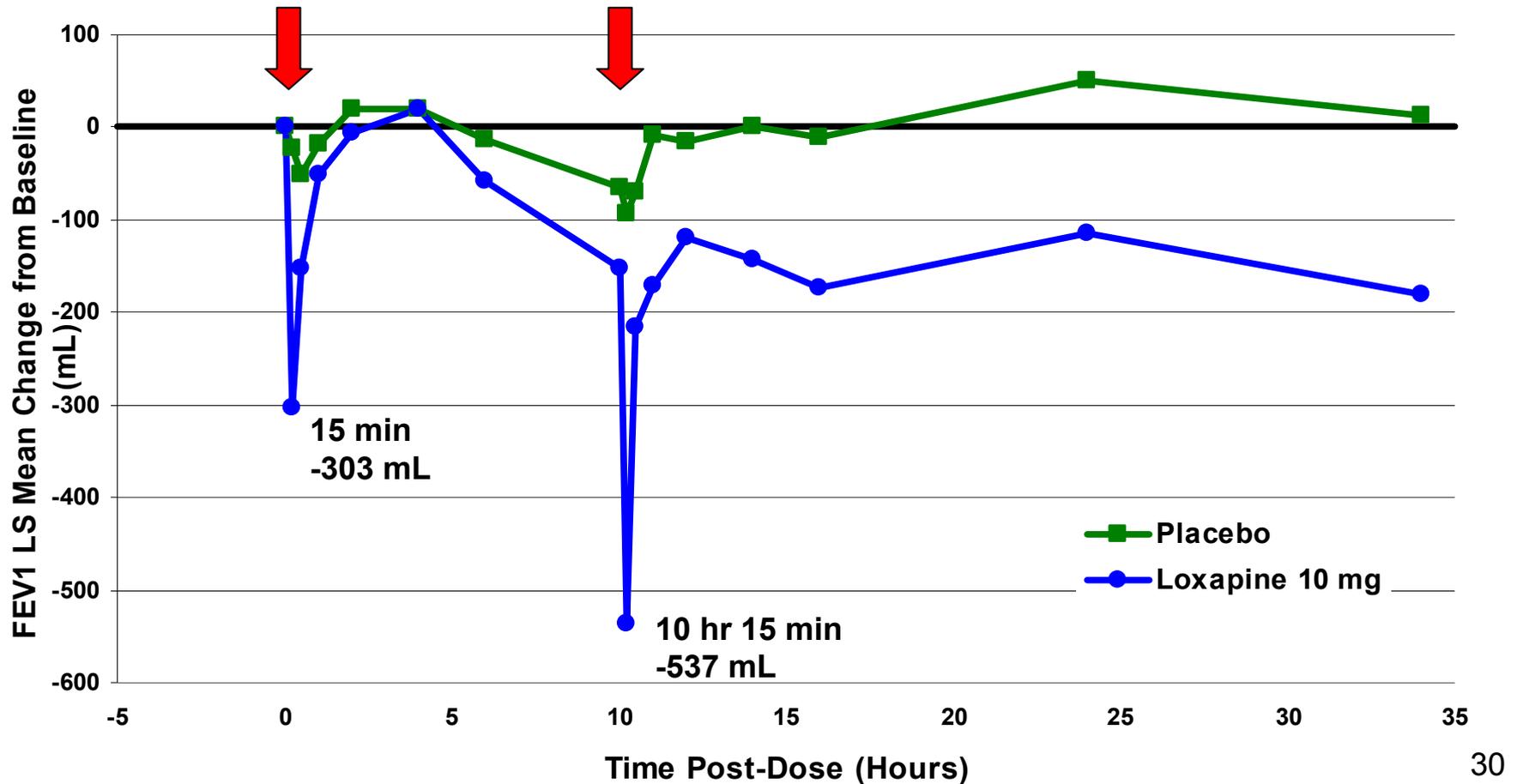
Maximum FEV1 Decrease

Maximum FEV1 decrease after either dose [†]	<i>Staccato</i> Placebo N=29 n (%)	<i>Staccato</i> Loxapine N=27 n (%)
≥ 10%	10 (34.5)	9 (33.3)
≥ 15%	1 (3.4)	6 (22.2)
≥ 20%	0	2 (7.4)

[†]FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

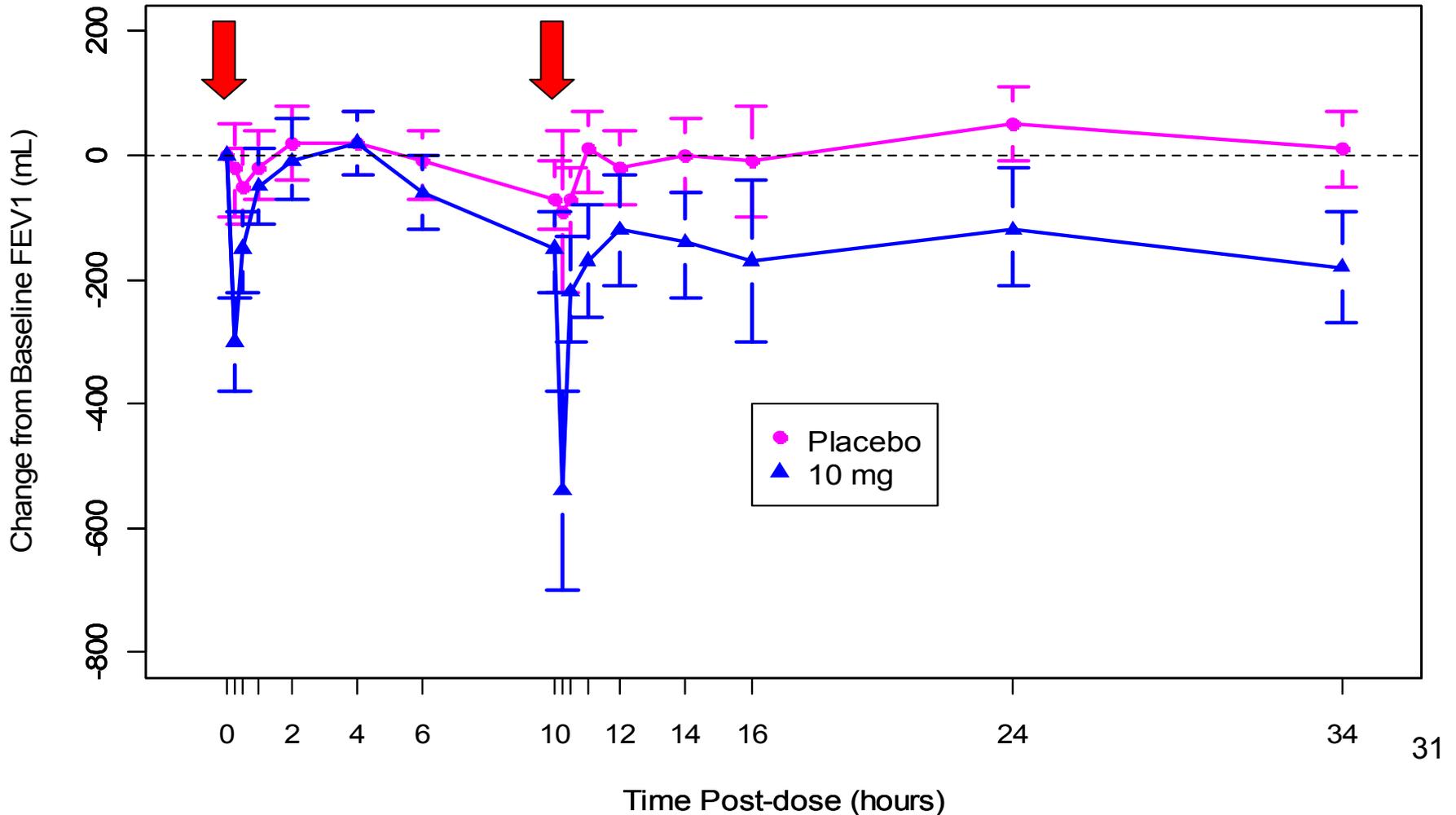
Trial 105: Asthma

LS Mean FEV1 versus Time



Trial 105: Asthma

LS Mean FEV1 versus Time



Trial 105: Asthma

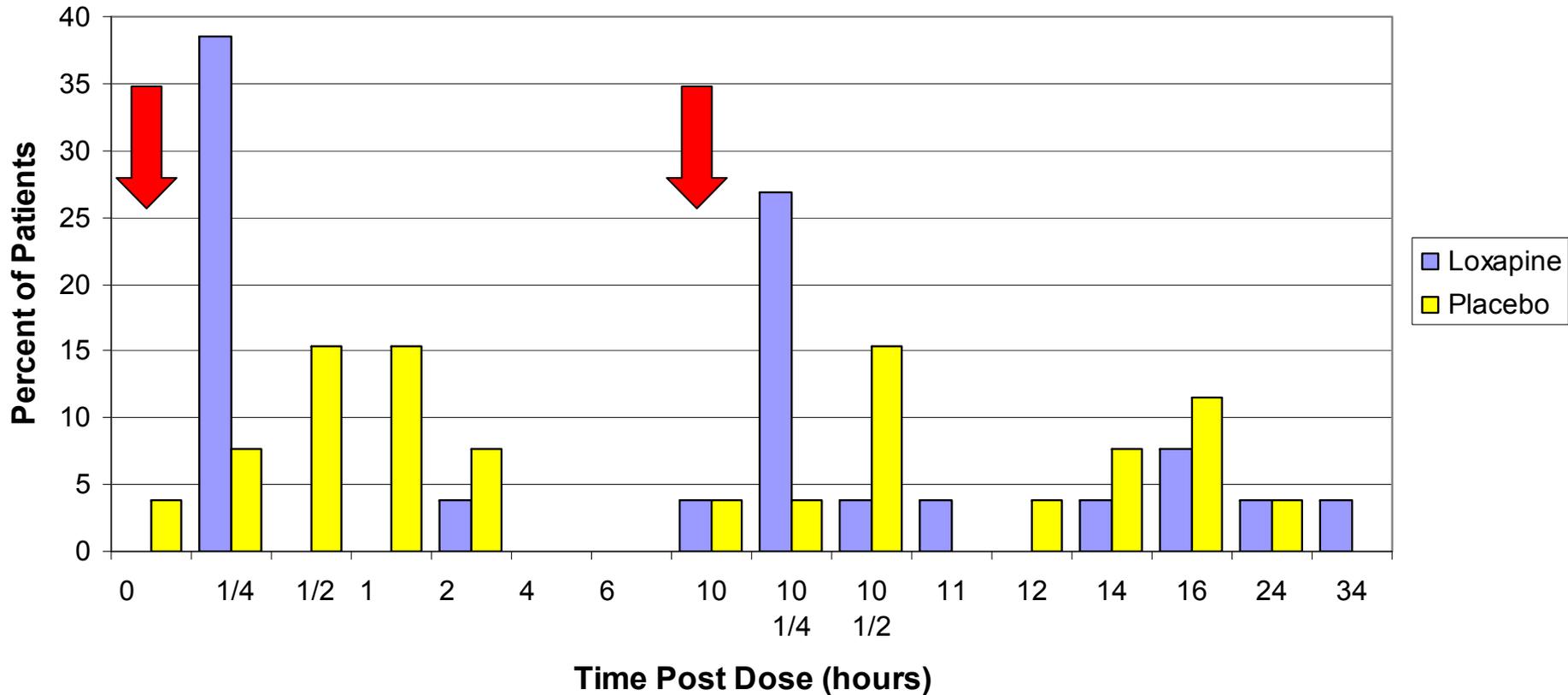
Maximum FEV1 Decrease

	Maximum % FEV1 Decrease [†]	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine
After either dose		N=26 n (%)	N=26 n (%)
	≥10%	3 (11.5)	22 (84.6)
	≥15%	1 (3.8)	16 (61.5)
	≥20%	1 (3.8)	11 (42.3)
After Dose 1		N=26	N=26
	≥10%	2 (7.7)	16 (61.5)
	≥15%	1 (3.8)	8 (30.8)
	≥20%	1 (3.8)	6 (23.1)
After Dose 2		N=25	N=17
	≥10%	3 (11.5)	12 (70.6)
	≥15%	1 (3.8)	9 (52.9)
	≥20%	1 (3.8)	5 (29.4)

[†]FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

Trial 105: Asthma

Timepoint of Minimum FEV1



Trial 105: Asthma

Airway Adverse Events

Adverse event	<i>Staccato</i> Placebo N=26 n (%)	<i>Staccato</i> Loxapine N=26 n (%)
Respiratory, Thoracic and Mediastinal Disorders	3 (11.5)	14 (53.8)
Bronchospasm	1 (3.8)	7 (26.9)
Chest discomfort	2 (7.7)	6 (23.1)
Cough	0	1 (3.8)
Dyspnea	0	3 (11.5)
Throat tightness	0	1 (3.8)
Wheezing	0	4 (15.4)

Trial 108: COPD

Maximum FEV1 Decrease

	Maximum % FEV1 Decrease [†]	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine
After either dose		N=27 n (%)	N=25 n (%)
	≥10%	18 (66.7)	20 (80.0)
	≥15%	9 (33.3)	14 (56.0)
	≥20%	3 (11.1)	10 (40.0)
After Dose 1		N=27	N=25
	≥10%	8 (29.6)	16 (64.0)
	≥15%	4 (14.8)	10 (40.0)
	≥20%	2 (7.4)	9 (36.0)
After Dose 2		N=26	N=19
	≥10%	15 (57.7)	12 (63.2)
	≥15%	6 (23.1)	10 (52.6)
	≥20%	1 (3.8)	5 (26.3)

[†]FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories

Trial 108: COPD

Airway Adverse Events

Adverse event	<i>Staccato</i> Placebo N=27 n (%)	<i>Staccato</i> Loxapine N=26 n (%)
Respiratory, Thoracic and Mediastinal Disorders	3 (11.1)	4 (15.4)
Bronchospasm	1 (3.7)	0
Cough	1 (3.7)	3 (11.5)
Dyspnea	1 (3.7)	3 (11.5)
Pulmonary congestion	0	1 (3.8)
Sinus headache	1 (3.7)	0
Throat irritation	1 (3.7)	0
Wheezing	0	2 (7.7)

Pulmonary Safety in Agitated Population

- Three Phase 2/3 trials
 - 787 patients total, 524 received loxapine, 196 received more than one dose
 - Screening 1-14 days prior to enrollment
 - Exclusion criterion: “clinically significant acute or chronic pulmonary disease (e.g. clinically apparent asthma, chronic bronchitis, emphysema)”
- 4 patients (0.76%) in loxapine group with airway-related AEs versus 0 in placebo
 - 2 patients wheezing, 1 cough → resolved
 - 1 patient discontinued 2° bronchospasm
- Number Needed to Harm \approx 131

Discontinuation due to Bronchospasm

- 59 year old female with schizophrenia
- Active smoker, 25 pack year history
- No history of asthma/COPD
- Received one dose of loxapine 10 mg
- 5 minutes later began wheezing, audible without a stethoscope
- No complaint of dyspnea
- Responded to albuterol MDI and oxygen

Discontinuation and Rescue Medication Use

Trial	Study Drug Discontinuation [†]		Rescue Medication Use	
	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine	<i>Staccato</i> Placebo	<i>Staccato</i> Loxapine
104: Healthy	0/30	1/30 (3.3)	0/30	0/30
105: Asthma	1/26 (3.8)	9/26 (34.6)	3/26 (11.5)	14/26 (53.8)
108: COPD	1/26 (3.8)	7/26 (26.9)	4/27 (14.8)	6/26 (23.1)
Ph2/3: Agitation [‡]	0/263	1/524 (0.2)	0/263	1/524 (0.2)

[†] due to respiratory AE or FEV1 decrease $\geq 20\%$

[‡] Trials 201, 301, and 302

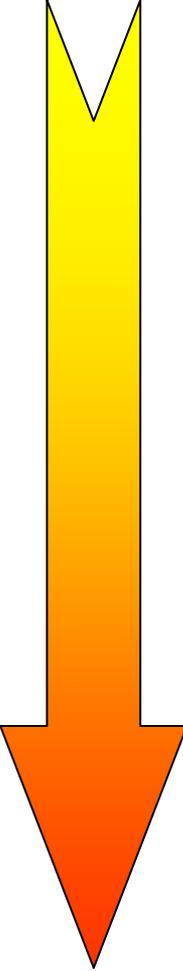
Population Factors Increasing Pulmonary Risks

- High prevalence of smoking
- May be unable to provide reliable history
- May not recognize symptoms of bronchospasm
- May be unable to use metered dose inhaler (MDI)
- Emergency settings may have limited access to records
- Psychiatric facilities may not have materials/staff on hand to treat bronchospasm
- Low socioeconomic status, illicit drug use, and psychiatric disease risk factors for asthma death ⁴⁰

Drug Factors Increasing Pulmonary Risks

- Loxapine is sedating, which may lead to decreased symptom reports and less wheezing on physical examination due to shallow breathing
- Proposed dosing up to every 2 hours, max 3 doses
 - Safety studies tested 2 doses 8-10 hr apart
- Additional doses may be given prior to full FEV1 recovery (14+ hours)

Treatment of Bronchospasm

- 
- **Mild** FEV1 $\geq 70\%$ predicted
 - Early recognition
 - Inhaled short-acting beta-agonists (SABAs) metered dose inhaler or nebulization
 - Removal of environmental factors
 - **Moderate** FEV1 40-69% predicted
 - **Severe** FEV1 $< 40\%$ predicted
 - Oxygen
 - SABA + ipratropium (repetitive nebulization)
 - Systemic corticosteroids
 - Adjunctive treatments (magnesium, heliox)
 - Intubation and mechanical ventilation

Mitigation Considerations

- Screen and do not administer if underlying respiratory condition
- Give only in health care setting with advanced airway management capabilities
- Monitor frequently with vital signs and physical examination; do not rely on patient report of symptoms
- For discussion
 - Can mitigation reduce risk to an acceptable level
 - Appropriate setting for administration
 - Monitoring requirements, duration, frequency
 - Safety of more than one dose

Summary and Conclusions

- Significant risk of bronchospasm
 - Worse in patients with underlying airway hyperresponsiveness
- Severity greater following second dose
- Does not return to baseline for >14 hours
- No regulatory precedent
- Characteristics of patient population and drug increase risk
- Risk-benefit determination for discussion

Risk Evaluation and Mitigation Strategy for Adasuve

(*Staccato* loxapine inhalation powder)

NDA 22-549

**Psychopharmacologic Drugs
Advisory Committee Meeting
December 12, 2011**

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Division of Risk Management

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Outline

- Introduction to REMS
- Steps for Safe Use of Loxapine Inhalation Powder
- Sponsor's Proposed REMS
- FDA Recommendations
- Additional REMS Options

Background

- For the majority of approved drugs, labeling and routine reporting requirements have been sufficient to mitigate risks and preserve benefits
- Some medications with serious risks have required additional risk mitigation strategies
- These strategies are referred to as Risk Evaluation and Mitigation Strategies (REMS)

What is a REMS?

- **Risk Evaluation and Mitigation Strategy**
- A required risk management plan that uses risk minimization strategies beyond professional labeling
- FDA can require a REMS if FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risks
 - Before approval
 - Post-approval if FDA becomes aware of **new safety information**
- REMS are enforceable

Food and Drug Administration Amendments Act (FDAAA) 2007

- Amended Food Drug and Cosmetic Act
 - Added section 505-1
- Authority to:
 - Require applicants to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) if necessary to ensure that the benefits of the drug outweigh its risks
- Applies to NDAs, ANDAs, and BLAs
 - Requirements differ slightly for ANDAs

Elements of a REMS

- A REMS **can** include:
 - Medication Guide or Patient Package Insert
 - Communication Plan for Health Care Providers
 - Elements to Assure Safe Use
 - May or may not be linked to some type of restricted distribution
 - Implementation System
- **Must** include a timetable for submission of assessments of the REMS

Medication Guide

- Provides FDA approved patient-friendly labeling
- Medication Guides (MG) as Part of REMS
 - FDA may approve a MG under 21 CFR part 208 without requiring a REMS
 - When MG as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 208.1
 - May be few occasions when MG will be included in the REMS

Communication Plan

- FDA approved materials used to aid sponsor's implementation of the REMS and/or inform healthcare providers about serious risks
 - Cannot be directed to patients
- Communication plan may include:
 - Dear Healthcare Professional letters
 - Dissemination of information to healthcare professionals through professional societies
 - Information about the REMS to encourage implementation
- When an ANDA is approved for a drug with a REMS that includes a communication plan, FDA must implement the communication plan

Elements to Assure Safe Use (ETASU)

- Requirements may include:
 - Healthcare providers who prescribe the drug have particular training or experience or special certification
 - Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
 - The drug may be dispensed only in certain healthcare settings
 - The drug may be dispensed to patients with evidence of safe-use conditions
 - Each patient must be subject to monitoring
 - Patients must be enrolled in a registry
- Are not mutually exclusive; in fact, there is considerable overlap

Drugs That Require ETASU

- The drug can only be approved or would be withdrawn unless such elements (to assure safe use) are required
- Assuring access and minimizing burden
 - Must be commensurate with specific serious risk(s) listed in the labeling
 - Cannot be unduly burdensome on patient access to the drug
 - To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs



Steps for Safe Use of Loxapine Inhalation Powder



Sponsor's Safe Use Checklist

ACTIVITY	RECOMMENDATIONS FOR SAFE USE
 SCREEN To identify appropriate ADASUVE patients	<input type="checkbox"/> Assess for acute respiratory signs/symptoms (eg, wheezing) <input type="checkbox"/> Inquire about current use of medications to treat asthma or COPD <input type="checkbox"/> Do not use in patients with acute respiratory signs/symptoms (eg, wheezing) or who are taking medications to treat asthma or COPD
 PREPARE To treat with ADASUVE	<input type="checkbox"/> Ensure that an inhaled short-acting beta-agonist bronchodilator (eg, albuterol) is readily accessible in the treatment setting <input type="checkbox"/> Review Instructions for Use provided on product pouch or in Full Prescribing Information <input type="checkbox"/> Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need for them to report symptoms
 OBSERVE Following treatment with ADASUVE	<input type="checkbox"/> Observe patient for 60 minutes post dose for signs and symptoms of bronchospasm
 MANAGE Bronchospasm if it occurs	<input type="checkbox"/> Patients who experience bronchospasm should be treated with an inhaled short-acting beta-agonist bronchodilator (eg, albuterol)

* Source: NDA 22549 Alexza Pharmaceuticals; m1.16 Risk Evaluation and Mitigation Strategy, August 4, 2100; Page 17.

FDA's Proposed Safe Use Checklist

Screen

- Ensure patients at known increased risk for loxapine inhalation powder induced bronchospasm do not receive the drug

Observe and Monitor

- Monitor patients appropriately post-dose to detect bronchospasm, should it occur

Prepare and Manage

- Ensure that appropriate treatment for bronchospasm is immediately available at the healthcare facility

Challenges to Screening

- Patients may be uncooperative and disorganized
- Patients may be unaware of any underlying pulmonary disease
- Emergency Departments may not have access to a patient medical history

Proposed Screening

1. Observe for acute respiratory signs and symptoms
2. Inquire if patient is currently taking medication to treat lung disease
3. Perform a physical exam including vitals and pulmonary exam

Challenges to Monitoring

- The risk of bronchospasm is unique with this treatment for agitation; therefore, standard practices that are used for monitoring patients after treatment of agitation may not be sufficient
- Sedated and/or agitated patients may not recognize or be capable of reporting physical symptoms of bronchospasm

Challenges to Monitoring

- Staff may have a difficult time recognizing signs of bronchospasm in an agitated or sedated patients
- Even patients with known asthma may poorly perceive the severity of airflow obstruction*

* National Asthma Education and Prevention Program, National Heart, Lung and Blood Institute, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007

Proposed Monitoring

1. Observe patients for a specified amount of time after each dose
2. Monitor every 15 min for the first hour and every 30 min, thereafter
3. Monitor vital signs and physical exam including chest auscultation
4. Ensure monitoring staff is capable of taking and interpreting monitoring requirements including chest auscultation

Challenges to Management

- A metered dose inhaler (short acting beta-agonist bronchodilator) can be difficult to use, especially, if a patient has no experience or is agitated or sedated
- If bronchospasm is not recognized early, it can progress to the stage of requiring advanced airway management capabilities

Proposed Management

1. Ensure availability of an inhaled, short acting beta-agonist bronchodilator in a metered dose inhaler
2. Ensure availability of nebulizer
3. Ensure immediate access to advanced airway management capabilities (i.e. intubation and ventilator)



Sponsor's Proposed REMS

Sponsor: REMS Components

- Medication Guide
- Communication Plan
- Healthcare Facility Certification (ETASU)

Sponsor: Medication Guide

- To be attached to the packaging of loxapine inhalation powder
- To be reviewed with the patient prior to administration under the supervision of a healthcare facility staff member

FDA Concerns: Medication Guide

- May not be practical to review with patients in an emergency room setting
- May not be practical or possible to review safety information with an agitated patient before treatment

Sponsor: Communication Plan

1. Dear Healthcare Provider Letter
2. Prescriber Brochure
3. Education Program (prescribers and healthcare facility staff)
4. Safe Use Checklist

FDA Concerns: Communication Plan

- For this serious risk, distributing educational materials to healthcare providers may not be sufficient
- Safe Use Checklist, as proposed, is not sufficient to assure safe use of the product
- Sponsor's proposal provides no assurance the Safe Use Checklist recommendations will be integrated into practice in a healthcare facility

Sponsor: Healthcare Facility Certification

HEALTHCARE FACILITY ENROLLMENT INFORMATION

Dear Healthcare Professional,

A healthcare facility must be enrolled in the ADASUVE Distribution Program in order to receive ADASUVE from the wholesaler / distributor. For each facility, an authorized healthcare facility representative is required to complete and sign the *Healthcare Facility Enrollment Form*.

Authorized Healthcare Facility Representative

A healthcare facility representative can be designated as *authorized* if he/she is able to attest to the criteria below. This may be a pharmacist, or another healthcare professional that has appropriate responsibility within the healthcare facility. The authorized healthcare facility representative will attest to the following on the *Healthcare Facility Enrollment Form*:

- He/she has received and read the *Healthcare Facility Enrollment Information Letter*.
- A short-acting beta-agonist bronchodilator (eg, albuterol) is readily accessible in the treatment settings within their healthcare facility.

After completing the form, submit it via:

- fax to 1-xxx-fax-xxxx, or
- email to ADASUVEdistribution@Alexza.com

Once the form is received, it will be entered into the ADASUVE Distribution Program Database, which is a secured database and accessed only by the wholesaler / distributor and Alexza Pharmaceuticals.

Ordering ADASUVE From Your Wholesaler / Distributor

When you place an order for ADASUVE through your wholesaler / distributor, they will check the database to confirm that your healthcare facility is enrolled. Once enrollment is confirmed, the wholesaler / distributor is allowed to ship ADASUVE to your facility.

If you have any questions about the enrollment process or ordering ADASUVE, please call 1-xxx-xxx-xxxx.

3 STEPS TO HEALTHCARE FACILITY ENROLLMENT

1. Read

An authorized healthcare facility representative should read this letter to become familiar with the healthcare facility enrollment process.

2. Complete and Sign

The healthcare facility representative completes the *Healthcare Facility Enrollment Form* on-line or prints and signs.

3. Submit

Submit via fax at:
1-xxx-fax-xxxx

Submit via email at:
ADASUVEdistribution@alexza.com

Note: Healthcare facilities must repeat the enrollment process every 3 years. You will be notified by fax or email 60 days prior to your re-enrollment date.

For important safety information, please see Full Prescribing Information, including Boxed Warnings.

Healthcare Facility (representative) will enroll and attest to the following:

- Has read Healthcare Facility Information letter
- Short-acting beta-agonist inhaler (albuterol) MDI will be available at the healthcare facility to treat bronchospasm

Form taken from Alexza proposed REMS submitted on

FDA Concerns: Healthcare Facility Certification

- No controls in place for treating bronchospasm that is not recognized early and progresses
- No assurance that patients will be screened, monitored and observed as recommended
- No assurance that practitioners have completed education about necessary screening and monitoring of patients

Anticipated Consequences

Bronchospasm may result in a severe patient outcome if:

- Patients are not adequately observed and monitored
- Appropriate treatment is not available to manage respiratory distress

Intention of a REMS for Adasuve

- To minimize the serious complications resulting from post-administration bronchospasm associated with loxapine inhalation powder
 - Observe and monitor patients appropriately
 - Ensure certified healthcare facilities have immediate access to advanced airway management capabilities



FDA's Recommendations: Minimum REMS Requirements

FDA: REMS Components

- **Communication Plan** targeting likely prescribers including psychiatrists and Emergency Department Physicians
- **Healthcare Facility Certification** including attestations to assure they are complying with REMS requirements

FDA: Communication Plan

- Communication plan components would remain the same as proposed by the sponsor
- **Safe Use Checklist** would be strengthened and recommendations would be incorporated into healthcare facility certification attestations
- **Education Program** could be used by healthcare facilities to accomplish required education of their staff

FDA: Healthcare Facility Certification

To become certified, a healthcare facility must attest to the following three steps:

1. Has or will establish procedures, protocols, and/or order sets to ensure REMS requirements are being met

Safe Use Checklist

1. **Screening**
 - Including physical exam
2. **Observing and Monitoring**
 - Observe patients for a specified amount of time after last dose of medication
 - 15 min for 1st hour & every 30 min thereafter
 - vitals and physical exam, including chest auscultation

FDA: Healthcare Facility Certification

To become certified, the healthcare facility must attest to the following:

2. Has immediate access to advance airway management capabilities (i.e. intubation and ventilator)
3. Will ensure that relevant staff are trained on safe use of loxapine inhalation powder - training records auditable

Education and Training

- For prescribers, nurses, monitoring staff, or pharmacists
- Could be web-based, in-services, etc.

Impact of Strengthening the REMS

- Increases assurance that:
 - Proper screening and monitoring will occur, through facilities establishing policies, procedures, and/or order sets
 - Bronchospasm that is not recognized and/or progresses can be effectively treated
 - Healthcare providers have completed education and training about necessary screening and monitoring of patients

Impact of Strengthening the REMS

- Further limits the settings in which loxapine inhalation powder would be available
- May limit patient access to medication
- Adds to burden on healthcare facilities
 - However, maintains healthcare facilities' flexibility in how they implement these controls (protocols, education, and order sets)

Limitations of REMS

- Attesting to meeting the requirements of the REMS does not guarantee the healthcare facilities will adhere to these requirements
- Requiring monitoring of agitated patients in an emergency department does not guarantee a patient will not leave against medical advice
- Screening is imperfect and will be more difficult in the intended patient population

Summary of the Proposed REMS

- The sponsor's proposal will not sufficiently mitigate the serious patient outcomes that could result from post-administration bronchospasm associated with loxapine inhalation powder.
- At a minimum, attestations need to be strengthened to enhance screening, monitoring, and treatment requirements
- Additional REMS controls may be considered

	Sponsor's Proposal	FDA's Proposal (additions to Sponsor proposal)
Healthcare Facility (HCF) Certification: Attestations	<ul style="list-style-type: none"> ➤ HCF representative has read the Healthcare Facility Information Letter ➤ Short acting beta-agonist bronchodilator metered dose inhaler will be available at the HCF to treat bronchospasm 	<ul style="list-style-type: none"> ➤ HCF will establish procedures, protocols and/or order sets to ensure REMS requirements are being met ➤ HCF has immediate access to advance airway management capabilities (i.e. intubation and ventilator) ➤ HCF ensures that relevant staff are trained on safe use of loxapine - training records auditable
Screen	<ul style="list-style-type: none"> ➤ Observe for acute respiratory signs and symptoms ➤ Inquire if a patient is taking medication to treat asthma or COPD 	<ul style="list-style-type: none"> ➤ + Physical exam (including pulmonary assessment) ➤ + Consider screening for additional risk factors
Prepare	<ul style="list-style-type: none"> ➤ Ensure availability of short acting beta-agonist bronchodilator metered dose inhaler 	<ul style="list-style-type: none"> ➤ + Ensure availability of nebulizer ➤ + Ensure immediate access to advanced airway management capabilities (i.e. intubation and ventilator)
Observe	<ul style="list-style-type: none"> ➤ Observe for 60 minutes post-dose for signs and symptoms of bronchospasm (focus on patient self-report) 	<ul style="list-style-type: none"> ➤ + Observe patients post-dose for specified amount of time ➤ + Monitor every 15 min for 1st hour & every 30 min thereafter ➤ + Monitor respiratory and heart rate and chest auscultation ➤ + Ensure monitoring staff is capable of taking and interpreting vitals
Manage	<ul style="list-style-type: none"> ➤ Treat bronchospasm with inhaled short-acting beta-agonist bronchodilator metered dose inhaler 	<ul style="list-style-type: none"> ➤ + Ensure availability of nebulizer ➤ + Ensure immediate access to advanced airway management capabilities (i.e. intubation and ventilator)

Voting Questions

- Does the committee conclude that Adasuve (loxapine) inhalation powder has been shown to be acceptably safe for use as a treatment for agitation in patients with schizophrenia or bipolar mania:
 - When used in conjunction with the REMS proposed by the sponsor?
 - When used in conjunction with the REMS proposed by FDA?



Additional REMS Options Specified in FDAAA

Additional REMS Options

- Add prescriber certification
- Limit access to certain healthcare settings
- Add monitoring requirement
- Add patient registry

Prescriber Education/Certification

- Prescriber certification required in order to prescribe loxapine
 - Prescribers would review education materials, and enroll;
 - Enrollment would be captured in a centralized REMS database
- Certification would be linked to dispensing
 - Option 1: Pharmacies would check REMS database prior to dispensing
 - Option 2: Healthcare facility would receive lists of currently enrolled prescribers so this information could be captured in their own management systems

Prescriber Education/Certification

Advantage

- Further ensures prescribers have completed education about necessary screening and monitoring of patients or management of bronchospasm

Disadvantages

- May be impractical to implement verification of prescriber certification in an emergency situations and may result in delays in treatment
- Adds burden to prescribers and healthcare facility
- May negatively impact the number of eligible prescribers thereby leaving certain patients without access to a drug

Limit Access to Specific Health Care Settings

- Only certain health care settings (e.g. emergency departments, hospitals) would be able to register as certified healthcare facilities. Therefore, loxapine inhalation powder would only be administered in these facilities.

Limit Access to Specific Health Care Settings

Advantage

- Increases the likelihood loxapine inhalation powder will only be administered in healthcare facilities that have routine close monitoring as well as immediate access to advanced airway management capabilities

Disadvantages

- Further limits the number of healthcare facility that will be able to utilize this medication; limits access at other facilities that may be capable of complying with established risk mitigation requirements
- Would require pre-defining which facilities qualify. For example, whether urgent care centers, direct admission psychiatric facilities, or nursing homes would qualify as either emergency departments or hospitals

Monitoring Requirement

- Healthcare facility staff would document administration, length of patient observation after administration of treatment, monitoring results, and any adverse events
- Documentation would be auditable and/or healthcare facility staff could be required to submit forms periodically

Monitoring Requirement

Advantages

- Increases likelihood that patients are being observed and monitored as recommended
- Data capture can improve characterization of risks

Disadvantages

- Adds burden to the healthcare facility
- Does not ensure patients won't leave before the observation period is complete even with this requirement
- HIPAA, patient privacy

Patient Registry

- Patients would be required to consent to being enrolled in the patient registry prior to receiving loxapine inhalation powder
- The registry could be designed to capture information including patient medical history, monitoring data, and patient outcomes

Patient Registry

Advantage

- May lead to better characterization of risk in the intended patient population thereby validating current or informing new screening and monitoring criteria

Disadvantages

- Requires consent of an agitated patient
- Reduces patient access; patients who are unwilling or unable to consent to participate in the registry would not be able to receive loxapine inhalation powder
- Adds burden to healthcare facilities
- May not be feasible in emergency departments
- Possible delays in treatment for agitated patients
- HIPAA, patient privacy

Conclusions

- Additional controls can be considered to increase the safe use of loxapine inhalation powder
- With additional controls, additional burden to the healthcare system and decreased patient access must be considered