Inhaled Loxapine (ADASUVE)

National Drug Monograph

February 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Inhaled loxapine is a typical antipsychotic used in the treatment of acute agitation associated with schizophrenia and bipolar I disorder in adults. Loxapine's mechanism of action for reducing agitation in schizophrenia and bipolar I disorder is unknown. Its effects are thought to be mediated through blocking postsynaptic dopamine D_2 receptors as well as some activity at the serotonin 5-HT_{2A} receptors.
Indication(s) Under Review in this document (may include off label)	Inhaled loxapine is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. **Off-label use** Agitation related to any other cause not due to schizophrenia and bipolar I disorder.
Dosage Form(s) Under Review	10mg oral inhalation using a new STACCATO inhaler device.
REMS	☐ REMS ☐ No REMS ☐ Post-marketing Study Required *See Other Considerations for additional REMS information*
Pregnancy Rating	C

Executive Summary	
Efficacy	• Inhaled loxapine was superior to placebo in reducing acute agitation at 2 hours post dose measured by the Positive and Negative Syndrome Scale-Excited Component (PEC) in patients with bipolar I disorder and schizophrenia. • Inhaled loxapine was twice as effective at reducing agitation than placebo 10 minutes post dose measured by the PEC in patients with bipolar I disorder and schizophrenia. • Inhaled loxapine showed improvements in agitation at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes) compared to placebo measured by the PEC in patients with bipolar I disorder and schizophrenia. • Inhaled loxapine was superior to placebo in reducing agitation 2 hours post dose measured by the Clinical Global Improvement scale. • There are no clinical trials comparing inhaled loxapine to agents currently utilized for the management of acute agitation (e.g., antipsychotics and benzodiazepines). It is unknown whether inhaled loxapine offers any advantages over standard treatments. • Patients involved in the clinical trials were assessed to have moderate to moderate-severe agitation and capable of providing informed consent prior to administration of inhaled loxapine. Patients who were severely agitated may not

	have been able to give informed consent and therefore were excluded from the clinical trials. The applicability of inhaled loxapine in a real world clinical setting is unknown. • The quality of the evidence for inhaled loxapine for agitation in schizophrenia and bipolar disorder is moderate.
Safety	• Safety for inhaled loxapine is available from 2 phase III and one phase II clinical trials each with a 24 hour observation period. The most common adverse reactions were dysgeusia, sedation and throat irritation. • Less than 1% of patients treated with inhaled loxapine experienced extrapyramidal symptoms compared to placebo. Additionally, inhaled loxapine did not prolong the QTc interval. • Inhaled loxapine is contraindicated in patients with clinically significant acute or chronic pulmonary disease (e.g., asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema) due to a potential increase in bronchospasm. • Inhaled loxapine has two boxed warnings pertaining to bronchospasm and increased mortality in elderly patients with dementia-related psychosis. • Severe hypotension requiring vasopressor treatment should be managed with norepinephrine or phenylephrine, and not epinephrine which may worsen the hypotension.
Potential Impact	• Current guidelines cite speed of onset as one of the most important factors in choosing a route of administration for treatment of agitation. Although intramuscular formulations have a faster onset, oral drugs should be offered to patients before considering an intramuscular formulation. Guidelines recommend that first or second generation antipsychotics be used as first line agent alone or in combination with a benzodiazepine. Benzodiazepines may be used first line when it is unclear of the underlying medical condition or for agitation caused by intoxication. • Inhaled loxapine was studied as a first line agent for agitation in clinical trials. Inhaled loxapine has a rapid onset of action and showed a reduction in agitation within 10 minutes compared to placebo. Inhaled loxapine may serve as a non-invasive treatment alternative to agitated patients who refuse oral and intramuscular medications. • Inhaled loxapine was well tolerated by patients in clinical trials and readily accepted by patients with acute agitation. In clinical trials, patients' baseline PEC and CGI-S scores were approximately 17 and 4, indicating moderate agitation. • Health facilities wishing to dispense and administer inhaled loxapine must be enrolled and comply with the REMS requirements.

Background

Purpose for review

Recent FDA approval

Issues to be determined:

- What is the evidence of need?
- Does inhaled loxapine offer advantages to currently available alternatives?
- Does inhaled loxapine offer advantages over current VANF agents?
- What safety issues need to be considered?
- Does inhaled loxapine have specific characteristics best managed by the non-formulary process, prior authorization, or criteria for use?

Other therapeutic options

Formulary Alternatives (IM short acting)	Other Considerations (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
Aripiprazole	Sedation and orthostatic hypotension
Chlorpromazine	Sedation, anticholinergic effects
Fluphenazine	Extrapyramidal side effects, sedation, anticholinergic effects
Haloperidol	Extrapyramidal side effects, QTc prolongation
Lorazepam	No antipsychotic effect, potential for respiratory depression, treats alcohol withdrawal
Olanzapine	Favorable extrapyramidal symptom profile, concomitant administration of intramuscular benzodiazepines is not recommended due to the potential for excessive sedation and cardiorespiratory depression
Ziprasidone	QTc prolongation
Formulary Alternatives (PO)	**Other Considerations**
Aripiprazole	
Haloperidol	
Lorazepam	
Olanzapine	

Efficacy (FDA Approved Indications)[1-4, 8,10,11]

Literature Search Summary
A literature search was performed on PubMed/Medline (2010 to October 2014) using the search terms inhaled loxapine, and ADASUVE. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy
The FDA approved inhaled loxapine 10mg for the treatment of acute agitation in adults with schizophrenia and bipolar I disorder based on three pivotal manufacturer sponsored randomized controlled trials (one phase II trial and one phase III trial in schizophrenia, and one phase III trial in bipolar I disorder).

Outcome measures were similar for all trials that were used to evaluate inhaled loxapine versus placebo in the treatment of acute agitation in schizophrenia and bipolar I disorder. Psychometric scales that were used to assess agitation in the trials were the Positive and Negative Syndrome Scale Excited Component (PEC) and the Clinical Global Impression Improvement (CGI-I) Scale.

Efficacy measures:
The PEC is an instrument that helps assess agitation using 5 items: poor impulse control, tension, hostility, uncooperativeness and excitement. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme).

Scores can range from a low score of 5 (all symptoms absent) to a high score of 35 (all symptoms extreme). Scores that are ≥ 20 are considered to be severe. Patients enrolled in the trials had to have a PEC score of ≥14, with at least one individual item score ≥ 4 Patients in both trials were assessed for agitation at 10, 20, 30, 45 minutes, and at 1, 1.5, 2, 4, and 24 hours after inhalation. The primary endpoint for both trials was the change from baseline PEC score 2 hours after dosing with inhaled loxapine or placebo. Baseline measurements were obtained 30 minutes before treatment with inhaled loxapine or placebo.

The key secondary endpoint for all trials was the CGI-I score 2 hours post dose with inhaled loxapine or placebo. The CGI-I is a global assessment of symptom improvement from baseline measurement with the Clinical Global Improvement-Severity scale (CGI-S). The CGI-I is scored on a scale of 1 (very much improved) to 7 (very much worse). Patients were assessed at baseline for agitation with the CGI-S with scores that range from 1 (normal), 4 (moderately ill), to 7 (extreme agitation).

Additional endpoints that were collected included: changes from baseline in the PEC at different time points between 10 minutes and 2 hours, time to second dose and response rate according to the CGI-I.

Schizophrenia
Level of Evidence: Moderate

Allen et al (2011) conducted a phase II, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of inhaled loxapine 5mg (n=45) and 10mg (n=41) compared to placebo (n=43) in patients with acute agitation (determined by the PEC) associated with schizophrenia and schizoaffective disorder (per DSM-IV criteria). The primary endpoint was the change from baseline on the PEC two hours after administration of the inhaled product.

- Compared with placebo, loxapine 5mg and 10mg significantly improved PEC scores 2 hours after administration. The 10mg and 5mg dose of inhaled loxapine showed a change in PEC score of -8.56 (p=.0002), -6.71 (p=0.088) compared to placebo at -4.97 respectively, at 2 hours after administration. Change in PEC was also evaluated at specific time points (10, 20, 30, 45, 90 minutes and 2, 3, and 24 hours) over the 24 hour period after administration of inhaled drug. The 10mg group separated from the placebo group at 20 minutes post inhalation ($p<0.05$). The 5mg group approached significance at the 45 minute time point (p=.051). The results for the 5mg group fell intermediately between the results of the 10mg group and placebo suggesting a dose-response relationship.
- Inhaled loxapine was also significant at reducing agitation as measured by a variety of secondary outcome measures (change from baseline on the PEC by time point over the 24 hours after administration, change at 2 hours after administration on the Clinical Global Impressions- Improvement scale (CGI-I), change from baseline on the Behavioral Activity Rating Scale (BARS)). Scores on the CGI-I at 2 hours after inhalation of loxapine showed significant effects of the 10mg (p= .0003) and 5mg (p= .0067) doses as well as responder analysis based on CGI-I scores. Of the 43 patients in the placebo group, only 9 were CGI-I responders as compared with 22 of those in the 5mg loxapine group and 25 of those in the 10mg loxapine group.
- There was also an approximate -2.0 difference between treatment and placebo in the change from baseline on the BARS scores at the 2 hour time point after inhalation of 10mg ($p <0.0001$) but not the 5mg group. Both groups of inhaled loxapine also showed a significant difference from placebo in time to administration of first rescue medication.
- Per the protocol, no groups received rescue medication within the first 2 hours. After 4 hours no patients in the 10mg loxapine group received any rescue medication compared to 4.4 % of those in the 5mg loxapine group and 7% in the placebo group. At the end of the 24 hour observation period, 33% of the placebo group had received rescue medication compared with 11% in the 5mg loxapine group and 15% in the 10mg loxapine group. Based on the PEC and BARS scores, inhaled loxapine showed a sustained response of action at 2 hours post inhalation.

Lesem et al. (2011) conducted a phase III, double-blind, randomized placebo-controlled trial to evaluate inhaled loxapine for the acute treatment of agitation in schizophrenia. Three hundred and forty-four patients, aged 18-65 years old, were randomized to receive 5mg of inhaled loxapine, 10mg of inhaled loxapine or placebo for up to 3 doses being administered in a 24-hour period. The primary endpoint was the change from baseline (approximately 17.8 and 17.6 for the 5mg and 10mg inhaled loxapine groups, respectively and 17.4 for placebo) in the PEC score 2 hours after one inhalation of loxapine compared to the change in scores from baseline in the placebo group.

- At 2 hours post inhalation the overall treatment effect of loxapine separated from placebo ($p < .0001$). Both the 5mg and 10mg loxapine doses resulted in significantly larger decreases (approximately -7.6 and -8.7, and -5.6 respectively) in the PEC compared to placebo (5mg $p=0.0004$; 10mg $p < 0.0001$). A continued treatment effect for both strengths of loxapine was seen at all measured time points throughout the 24 hour period after one dose of inhaled loxapine.

- The key secondary efficacy measure compared CGI-I score at 2 hours after one dose of inhaled loxapine to placebo. Both the 5mg and 10mg loxapine groups showed a statistically significant decrease in agitation compared to placebo.
- A score of 2 signified much improved and 3 signified minimally improved on the CGI-I scale. Baseline CGI-I scores were 3.9, 4.0, and 4.1, and declined to 2.3, 2.1 and 2.8, respectively, for the placebo and 5mg and 10mg loxapine groups (5mg, $p=0.0015$; 10mg, $p < 0.0001$).
- Kaplan-Meier survival analysis of the time to second dose was also studied. The overall difference favored the inhaled loxapine groups over the placebo group and this was statistically significant ($p=0.029$). When separated individually only the 10mg loxapine group showed a statistical significance compared to placebo in time to second dose ($p=0.0076$).

Bipolar I disorder
Level of Evidence: Moderate

Kwentus et al. (2012) conducted a phase III, randomized, double blind, placebo-controlled parallel group inpatient study to evaluate inhaled loxapine for the treatment of acute agitation in patient with bipolar I disorder. The study randomized 314 patients, aged 18-65 years old, in a 1:1:1 fashion to receive inhaled loxapine 5mg or 10mg, or inhaled placebo to be assessed for a 24 hour period.

- The overall treatment effect was statistically significant ($p <0.0001$) and significantly larger decreases compared to placebo were seen for the 5mg group ($p <0.0001$) and 10mg groups ($p <0.0001$). PEC scores were also compared at multiple times points throughout the 24 hour assessment period. The inhaled loxapine groups produced a rapid onset of effect at the 10 minute time point after one dose, which showed a significant difference for both loxapine groups compared to placebo ($p < 0.0001$ for both loxapine groups). A continued treatment effect was evident at all times points through 24 hours after one dose of loxapine.
- The key secondary endpoint of CGI-I score at 2 hours after first inhalation of loxapine showed significant decreases in agitation compared to placebo ($p <0.0001$). CGI-I responder analysis 2 hours after administration of inhalation also showed that significantly more of the loxapine patients (both 5mg and 10mg) were rated as very much improved or much improved compared to placebo ($p < 0.0001$). The number needed to treat (NNT) for the 5mg group was 2.58 and 2.14 for the 10mg group.
- Time to a second as needed dose of loxapine was evaluated using a Kaplan-Meier survival analysis. Overall, there was a significant difference favoring the loxapine groups over the placebo group ($p <0.0001$). Both the 5mg and 10mg loxapine groups showed significance when compared individually to placebo in time to second dose ($p=0.0058$ and $p <0.0001$ respectively).

Systematic Review
Citrome (2012) evaluated the efficacy and adverse effects of inhaled loxapine in the treatment of agitation in patients with schizophrenia and bipolar I disorder. Two phase III trials (discussed above) were included in the review. The mean differences observed with inhaled loxapine versus placebo on agitation in patients with schizophrenia or bipolar I disorder can be found in Appendix A. The authors concluded that inhaled loxapine had a

medium effect size (5mg=0.45, 10mg=0.60) against placebo on the PEC at 2 hours after first dose for patients with schizophrenia. Effect size differences for the secondary measure of CGI-I scores at 2 hours were similar at 0.45 for the 5mg group and 0.63 for the 10mg group. The (NNT) for PEC response and CGI-I response versus placebo were 4.1 and 4.6, respectively, for loxapine 5mg, and 3.2 and 3.2, respectively for the 10mg dose of loxapine. For patients with agitation with bipolar I disorder, the authors concluded that inhaled loxapine had a large effect size (5mg=0.73, 10mg=0.94) against placebo on the PEC at 2 hours after first dose. Effect size differences for the secondary measure of CGI-I at 2 hours after first dose were higher (5mg=0.84, 10mg=1.02). For both measures, the PEC and CGI-I, the effect sizes were larger than what was observed in the trial with schizophrenia. NNT for PEC and CGI-I response were 2.9 and 2.6 respectively, for the loxapine 5mg group and 2.2 and 2.1, respectively, for the 10mg group. Inhaled loxapine appeared to be effective in reducing agitation in patients with schizophrenia or bipolar I disorder and was well tolerated in the study population.

Summary

All three trials found that inhaled loxapine significantly reduced agitation compared to placebo using the primary endpoint of change in baseline PEC score at 2 hours post inhalation. The secondary endpoint of CGI-I score 2 hours post inhalation was also significantly improved for the inhaled loxapine groups in all trials.

Inhaled loxapine showed a statistically significant difference at reducing agitation compared to placebo at 10 minutes on the PEC scale. In patients with schizophrenia, 39% of the total effect of inhaled loxapine was observed at 10 minutes, which represented a 20% reduction from baseline. In the bipolar I population, 43% of the total effect of inhaled loxapine was observed at 10 minutes, which represented a 23% reduction from baseline. In both studies inhaled loxapine showed a statistical difference compared to placebo at all assessment time points up to 2 hours.

Standard of care for agitated patients according to the Expert Consensus Guidelines for Treatment of Behavioral Emergencies, is to use an antipsychotic or benzodiazepine, either by an oral formulation or intramuscular injection. The guidelines also cite that speed of onset is one of the most important factors in choosing a route of administration. Oral formulations are slowed due to absorption parameters and intramuscular formulations may take up to 15-60 minutes to take effect. Some patients may be hesitant to receive intramuscular injections as well and during this time symptoms can increase and put patients and staff at risk. Inhaled loxapine offers a new, non-invasive, rapid acting alternative to oral and intramuscular formulations to reduce agitation associated with schizophrenia and bipolar I disorder. Studies demonstrated a favorable patient response to inhaled loxapine, as no dose was refused by any patient.

Inhaled loxapine is contraindicated for use in patients with asthma and COPD. All three studies excluded patients with a history of asthma or COPD. This limits generalizability to the VA patient population, which often presents with multiple comorbid conditions such as asthma and COPD.

Potential Off-Label Use

- All cause agitation not in the setting of schizophrenia or bipolar I disorder.

Safety 1-4,9

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	**Bronchospasm** Inhaled loxapine can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer inhaled loxapine only in enrolled healthcare facility that has immediate access on –site to equipment and personnel trained to manage acute bronchospasm, including advanced

	airway management (intubation and mechanical ventilation). Prior to administering inhaled loxapine, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest ausculation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with inhaled loxapine. Because of the risk of bronchospasm, inhaled loxapine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS. **Increased Mortality in Elderly Patients With Dementia-Related Psychosis** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Inhaled loxapine is not approved for the treatment of patients with dementia-related psychosis
Contraindications	• Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm • Acute respiratory signs/symptoms (e.g., wheezing) • Current use of medications to treat airways disease, such as asthma or COPD • History of bronchospasm following inhaled loxapine treatment • Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine.
Warnings/Precautions	• Inhaled loxapine can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. See Boxed Warning above. Due to the risk of bronchospasm, inhaled loxapine is available only through a restricted program under REMS called the ADASUVE REMS. Required components of the ADASUVE REMS are: o Healthcare facilities that dispense and administer inhaled loxapine must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site access to equipment and personnel trained to provide advance airway management, including intubation and mechanical ventilation. o Wholesalers and distributors that distribute inhaled loxapine must enroll in the program and distribute only to enrolled healthcare facilities. • Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. • Neuroleptic malignant syndrome may develop in patients treated with antipsychotic drugs. NMS did not occur in the inhaled loxapine program. • Inhaled loxapine can potentially cause hypotension, orthostatic hypotension, and syncope. Caution should be used in patients with known cardiovascular or cerebrovascular disease, or patients predisposed to hypotension. In the presence of severe hypotension requiring vasopressor therapy, the preferred drugs may be norepinephrine or phenylephrine. Epinephrine should not be used because of beta stimulation may worsen hypotension in the setting of inhaled loxapine induced partial alpha blockade. • Inhaled loxapine has the ability to lower the seizure threshold. Use with caution in patients with a history of seizures or with conditions that lower

	the seizure threshold. • Use caution when driving or operating machinery. Inhaled loxapine can impair judgment, thinking and motor skills. The potential for cognitive and motor impairment can be enhanced if inhaled loxapine is administered concurrently with other CNS depressants. • Inhaled loxapine does have anticholinergic activity, and has the potential to cause anticholinergic adverse reactions. Concomitant use of multiple anticholinergic drugs could have additive effects.

Safety Considerations

- Overall inhaled loxapine was well tolerated by patients in clinical trials. Adverse events were reported if ≥ 2% of patients in any treatment group experienced an adverse event. The most common adverse events reported were dysgeusia, sedation, and throat irritation for patients who received inhaled loxapine. In both clinical trials of bipolar disorder and schizophrenia, there were few reports of airway adverse events, indicating a favorable pulmonary profile for the intended clinical population. One patient did have an acute bronchospasm that was relieved with an albuterol inhaler.
- Patients with respiratory illnesses such as asthma and COPD were excluded from the study population due to the potential for inhaled loxapine to cause bronchospasm. Two separate safety studies done by Gross et al, were performed in patients without psychiatric disease, who had asthma or COPD to evaluate the risk of bronchospasm associated with inhaled loxapine. The primary outcome of these studies was the change in FEV_1 from baseline. In a study of 26 patients with asthma who received two doses of 10mg of inhaled loxapine 10 hours apart, 30% of patients had a ≥20% decrease in their FEV_1. Fifty-four percent of patients given inhaled loxapine had respiratory adverse reactions and 54% required rescue albuterol. The second study evaluated the effect of inhaled loxapine on FEV_1 in patients with COPD. Twenty-five patients with COPD were given two doses of 10mg of inhaled loxapine 10 hours apart and had their FEV1 measured post dose. Twenty-six percent of patients experienced a ≥20% decrease in their FEV1. Nineteen percent of patients had respiratory adverse events and 23% required rescue albuterol.
- Inhaled loxapine, a first generation antipsychotic, does have the potential to cause extrapyramidal side effects. Although in clinical trials extrapyramidal side effects were not commonly reported, there were instances of them occurring and should be monitored for in patients receiving inhaled loxapine.

Adverse Reactions

Common adverse reactions	Dysgeusia (14%) Sedation (12%) Throat irritation (7%) Dizziness (5%) Dry mouth (5%)
Death/Serious adverse reactions	No reported deaths Dystonia Oculogyration Akathisia Severe sedation
Discontinuations due to adverse reactions	Out of 473 patients studied in schizophrenia, only one patient discontinued loxapine therapy due to an adverse reaction (bronchospasm). Out of 314 patients studied in bipolar I disorder, 2 patients discontinued loxapine therapy due to an adverse reaction (anxiety).

Drug Interactions

Drug-Drug Interactions

- The concurrent use of inhaled loxapine with other CNS depressants can increase the risk of respiratory depression, hypotension, profound sedation, and syncope. Dose reduction of CNS depressants should be considered if used concomitantly with inhaled loxapine.
- The concomitant use of inhaled loxapine and other anticholinergic drugs can increase the risk of anticholinergic adverse reactions including exacerbation of glaucoma and urinary retention.

Drug-food Interactions

- N/A

Drug-Lab Interactions

- N/A

Risk Evaluation

As of December 17, 2015

	Comments
Sentinel event advisories	• NONE
Look-alike/sound-alike error potentials	• Loxapine/Lexapro • Loxitane/Fluoxetine • Loxitane/Soriatane • ADASUVE/Advair • Loxapine/Amoxapine

Other Considerations[5]

During deliberations, although the FDA felt that inhaled loxapine had shown efficacy for treating acute agitation, they had concerns regarding potential to cause pulmonary toxicity in patients with asthma or COPD. The FDA had originally sent a complete response letter to the manufacturer citing their concerns and their suggestions on how to proceed, which included a REMS program. The initial dosing recommendation from the manufacturer was for every 2 hours as needed up to three doses in a 24 hour period. The FDA with their concerns for bronchospasm limited the dosing to just one administration in a 24 hour period. To an untrained observer, respiratory distress may be confused with acute agitation, as well as masked by the sedating effects of inhaled loxapine. Due to these concerns, inhaled loxapine is only available through a restricted program under REMS called the ADASUVE REMS. Required components of the REMS include: healthcare facilities that dispense and administer inhaled loxapine must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site access to equipment and personnel trained to provide advance airway management, including intubation and mechanical ventilation. Wholesalers and distributors that distribute inhaled loxapine must enroll in the program and distribute only to enrolled healthcare facilities. The REMS program will also inform healthcare professionals about the risk of bronchospasm after inhaled loxapine administration, appropriate patient selection, monitoring patients after administration and management of bronchospasms. Healthcare providers will also be required to check on patients every 15 minutes for at least an hour to assess for bronchospasm. The FDA also required for the manufacturer to perform a post marketing observational study to collect more safety data regarding bronchospasm in a real world setting.
From the ADASUVE REMS Web Site:
ADASUVE Healthcare Facility Enrollment

ADASUVE will be dispensed only to patients in healthcare facilities that are enrolled in the ADASUVE REMS Program.

Authorized Healthcare Facility Representative

For each healthcare facility, an authorized healthcare facility representative is required to complete and sign the Healthcare Facility Enrollment Form acknowledging that the enrolled healthcare facility meets specific requirements. This representative may be a pharmacist, or another healthcare professional with the appropriate level of responsibility within the healthcare facility, who is authorized to act on behalf of the facility.

Healthcare Facility Qualifications for Enrollment

The healthcare facility requirements include having the following:
•Immediate access onsite to equipment and personnel trained to provide advanced airway management, including intubation and mechanical ventilation
•Immediate access onsite to a metered-dose inhaled and nebulized form of a short-acting beta-agonist bronchodilator (eg, albuterol)
•Procedures, protocols, and/or order sets to ensure the following: —Patients are screened, prior to treatment with ADASUVE, for a history of pulmonary disease and for acute respiratory signs and symptoms by physical exam, including taking vital signs and chest auscultation, and inquiring if patient is taking medication to treat asthma or COPD
—Patients are monitored at least every 15 minutes for a minimum of 1 hour following treatment with ADASUVE for signs and symptoms of bronchospasm, including taking vital signs and chest auscultation
—Administration of ADASUVE is limited to 1 dose per patient within 24 hours

•Healthcare providers within the facility (prescribers, nurses, monitoring staff, or pharmacists) who are trained on the safe use of ADASUVE using the ADASUVE Education Program

Dosing and Administration[9]

- Inhaled loxapine must be administered only by a healthcare professional. Inhaled loxapine is administered by oral inhalation only. The recommended dose for acute agitation is 10 mg administer by oral inhalation, using a single-use inhaler. Administer only a single dose within a 24-hour period.
- Prior to administering inhaled loxapine, all patients should be screened for a history of asthma, COPD, or other pulmonary disease, and examine patients (including chest auscultation) for respiratory signs (e.g. wheezing).

- A**dministration (Refer to package insert for full administration information)**
    1. Open the pouch and remove inhaler. The indicator light will be off.
    2. Firmly pull plastic tab from the inhaler. Check for indicator light to turn green, inhaler must be used within 15 minutes.
    3. Explain the administration procedure to the patient prior to use.
    4. Instruct the patient to exhale fully.
    5. Instruct the patient to put the mouthpiece of the inhaler between the lips, close the lips, and inhale through the mouthpiece with a steady deep breath. Check that green light turns off indicating the dose have been delivered.
    6. Instruct patient to remove the mouthpiece from the mouth and hold their breath for as long as possible, up to 10 seconds.
    7. If the green indicator light remains on after the patient inhales, the dose of inhaled loxapine has NOT been delivered. Instruct the patient to repeat step 4, step 5, and step 6 up to 2 additional times. If the green light still does not turn off, discard the inhaler and use a new one.

Special Populations (Adults)

	Comments
Elderly	• No data identified
Pregnancy	• There are no adequate and well-controlled studies of inhaled loxapine use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptom following delivery. Loxapine, the active ingredient in ADASUVE, has demonstrated increased embryofetal toxicity and death in rat fetuses and offspring exposed to doses approximately 0.5-fold the maximum recommended human dose (MRHD) on a mg/m2 basis. Inhaled loxapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	• It is not known whether inhaled loxapine 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 inhaled loxapine, a decision should be made whether to discontinue nursing or discontinue inhaled loxapine, taking into account the importance of the drug to the mother.
Renal Impairment	• No dose adjustment necessary
Hepatic Impairment	• No dose adjustment necessary
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting),[4,7,8]

Agitation is a common characteristic of schizophrenia and bipolar mania and may potentially lead to patient and staff injuries. Agitation is the cause for 1.7 million emergency room visits in the United States annually. Agitation due to an underlying mental illness also leads to frequent admissions to an inpatient ward and continued hospitalization. A rapid, effective, and safe intervention that does not induce excessive sedation is important to help calm the agitation so further assessments can be made. The Best Practices in Evaluation and Treatment of Agitation project recommends that verbal de-escalation be the initial treatment for agitation. If patients do not de-escalate then patients should be encouraged to take oral medication voluntarily as opposed to forceful involuntary injections. The Expert Consensus Guidelines for Treatment of Behavioral emergencies cite speed of onset as one of the most important factors in choosing a route of administration. Intramuscular injections have the fastest onset (15-45 minutes) compared to oral medications (30-60 minutes). Second generation antipsychotics (e.g., olanzapine, ziprasidone and aripiprazole) are as efficacious as first generation antipsychotics (e.g., haloperidol and perphenazine) and are preferred due to side effect profiles. These agents can be used alone or in combination with a benzodiazepine. Inhaled loxapine has not formally been evaluated by any of the current guidelines. In clinical trials it has shown to be efficacious in the treatment of acute moderate to severe agitation and works quite rapidly compared to placebo. There are currently no other formulations similar to inhaled loxapine in terms of delivery systems. The clinical trial population was mostly male, in their early forties and current smokers. The study population was void of anyone with asthma or COPD due to an exclusion criterion for respiratory disease. The VA population tends to have a higher average age and often times patients present with multiple comorbidities including asthma and COPD. Extrapolating data from the studies, inhaled loxapine would have a potentially limited role in the VA population due to its contraindication in patients with asthma and COPD. Inhaled loxapine offers a non-invasive route of administration as well as a fast onset of action with a tolerable safety profile. The quality of the evidence for inhaled loxapine for agitation in schizophrenia and bipolar disorder is moderate. Based on review of the literature, inhaled loxapine is an option for treating acute agitation in patients with bipolar and schizophrenia. However, there are no comparative data of inhaled loxapine to any other agents used to treat agitation (e.g., antipsychotics, benzodiazepines). Applying this

information to clinical practice is difficult as a PEC scale is not used and often the agitation ratings are based on clinical judgment, which is not always consistent between clinicians. The clinical applicability will also be limited because inhaled loxapine will not replace IM treatments for severe agitation and by the facilities having to be pre-enrolled in the REMS program. Inhaled loxapine's advantages are its non-invasive delivery system, ease of use, and its ability to decrease agitation rapidly compared to placebo.

References

1. Allen M, Feifel D, Lesem M, Zimbroff D, Ross R, Munzar P, et al. Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72:1313-1321.
2. Lesem M, Tran-Johnson T, Riesenberg R, Feifel D, Allen M, Fishman R, et al. Rapid acute treatment of agitation in individuals with schizophrenia: multicenter, randomized, placebo-controlled study of inhaled loxapine. Br J Psychiatry. 2011;198:51-58.
3. Kwentus J, Riesenberg R, Marandi M, Allen M, Fishman R, Spyker J et al. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. Bipolar Disord. 2012;14:31-40.
4. Citrome L. Inhaled loxapine for agitation revisited: focus on effect sizes from 2 phase III randomized controlled trials in persons with schizophrenia or bipolar disorder. Int J Clin Pract. 2012;66:318-325.
5. US Food and Drug Administration. Adasuve ®(Loxapine) inhalation powder NDA 022549.: Psychopharmacolgoic Drug Advisory Committee Briefing Document. Mountain View, CA: Alexza pharmaceuticals; 2011. Available from:http://www.fda.gov/downloads/AdvisoryCommittess/CommittesMeetingMaterials/Drugs/PsychopharmacoloigcDrugsAdvisorCommittee/UCM282900/pdf. Accessed November 17, 2014.
6. Gross N, Greos LS, Meltzer EQ, Spangenthal S, Fishman RS, Spyker DA et al. Safety and tolerability of inhaled loxapine in sunjects with asthma and chonronic obstructive pulmonary disease—two randomized controlled trials. J Aerosol Med Pulm Drug Deliv. 2014;27:1-10.
7. Hollerman GH and Zeller SL. Overview of project BETA: Best practices in Evaluation and Treatment of Agitation. West J Emerg Med. 2012;13:1-2.
8. Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP. The expert consensus guidelines series. Treatment of behavioral emergencies 2005. J Psychiatr Pract. 2005;11 suppl1:5-108.
9. ADASUVE (inhaled loxapine) package insert. Teva Pharmaceuticals USA Inc. 2014.
10. Baker RW, Kinon BJ, Maguire GA et al. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. J Clin Psychopharmacol. 2003;23:342-348.
11. Busner J and Targum SD. The clinical global impression scale: Applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7)28-37.

Prepared January 2015 by Eric Johnson, PharmD; Chelsea Carr, PharmD; Colleen Hall, PharmD, BCPP; Matthew Fuller, PharmD, BCPP, BCPS, FASHP

Contact person: Todd Semla, MS, PharmD, BCPS, FCCP, AGSF

Appendix A: Clinical Trials

Table 1. Acute treatment of agitation in patients with schizophrenia with inhaled loxapine

Citation	Lesem M, Tran-Johnson T, Riesenberg R, Feifel D, Allen M, Fishman R, et al. Rapid acute treatment of agitation in individuals with schizophrenia: multicenter, randomized, placebo-controlled study of inhaled loxapine. Br J Psychiatry. 2011;198:51-58.
Study objective/purpose	Evaluate the efficacy and safety of inhaled loxapine for acute treatment of agitation in schizophrenia
Design	Phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study
Inclusion/Exclusion Criteria	**Inclusion** • 18-65 year old with schizophrenia (according to DSM-IV criteria) as applied by a research-trained psychiatrist on the basis of clinical presentation, psychiatric examination, known previously documented diagnosis when available, and history provided by a second source when available • Score of ≥ 14 (out of 35) and a score ≥ 4 (out of 7) on at least 1 of the 5 PEC items • Good general health as assessed by medical history, physical exam, 12-lead electrocardiogram, standard serum chemistry, hematology, and urinalysis • Nonpregnant and nonlactating females **Exclusion** • Agitation caused primarily by intoxication • Positive urine drug screen for psychostimulants • History of drug or alcohol dependence in past 2 months • Serious risk of suicide • Use of benzodiazepines or other hypnotics • Use of oral or short-acting IM antipsychotic drugs in the 4 hours before study treatment • Use of injectable depot neuroleptics within 1 dose interval before study treatment • Use of an investigational drug in the 30 days before screening • Clinically significant acute or chronic pulmonary disease • Clinically significant hepatic, renal, gastrenterologic, cardiovascular, endocrinologic, neurologic, or hematologic disease
Exposure	Baseline assessments, which were conducted 30 minutes before study treatment, were the PEC scale, the Clinical Global Impression-Severity scale (a pre-treatment assessment of agitation), the Agitation-Calmness Evaluation Scale (ACES, a scale developed by Eli Lilly and Company) and vital sign measurements. Eligible patients were then randomized 1:1:1 to the following treatments: • 10mg of inhaled loxapine • 5mg of inhaled loxapine • Inhaled placebo After randomization, dose one was administered and the 24-hour observation period began. If necessary, a maximum of three doses of the study drug were allowed during the 24-hour period, if agitation did not subside sufficiently after dose one or recurred, dose two could be given > 2 hours after dose one; if necessary, dose three could be given > 4 hours after dose two. Rescue medication (IM lorazepam) was not allowed until after the 2 hour assessments had been completed, dose two had been given, and at least 20 minutes had elapsed after

	the last dose of study drug, unless deemed medically necessary. During the 24-hour observation period, participants were not to receive any other psychotropic drug that, in the opinion of the investigator, would confound study efficacy or safety end-point. Drugs prescribed to treat extrapyramidal symptoms were prohibited as well.
Endpoints	**Primary** • Change from baseline in the PEC score 2 hours after dose one of inhaled loxapine compared with the change from baseline after inhaled placebo **Secondary** • Absolute CGI-I score 2 hours after dose one of inhaled loxapine compared with inhaled placebo • Changes from baseline in the PEC scores at each assessment time from 10 minutes through to 24 hours after dose one • Analysis of CGI-I responders at 2 hours • Time to Dose #2

Results

344 patients were randomized and all received at least one dose of the study drug (loxapine or placebo) and 338 completed the study.

Patient demographics

	Placebo (n=115)	Loxapine 5mg (n=116)	Loxapine 10mg (n=113)
Age, years			
Mean (s.d)	43.9 (9.45)	43.2 (10.24)	42.2 (9.82)
Median	45.0	44.5	44.0
Minimum, maximum	23.0, 63	18.0, 65.0	21.0, 62.0
Gender, n (%)			
Female	35 (30.4)	29 (25.0)	27 (23.9)
Male	80 (69.6)	87 (75.0)	86 (76.1)
Ethnicity, n (%)			
White	32 (27.8)	48 (41.4)	36 (31.9)
Black	70 (60.9)	61 (52.6)	67 (59.3)
Hispanic	9 (7.8)	6 (5.2)	8 (7.1)
Asian	4 (3.5)	1 (0.9)	1 (0.9)
Other	0	0	1 (0.9)
Smoking history, n (%)			
Never smoked	15 (13)	13 (11.2)	8 (7.1)
Current smoker	90 (78.3)	94 (81.0)	97 (85.8)
Ex-smoker	10 (8.7)	9 (7.8)	8 (7.1)
Diagnosis, years			
Mean (s.d)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)
Minimum, maximum	<1, 40	<1, 41	1, 49
Duration of current agitation episode, days			
Mean (s.d.)	6.9 (9.21)	6.1 (7.50)	7.6 (11.5)
Minimum, maximum	<1, 72	0, 45	<1, 90
Number of previous hospitalizations			
Mean (s.d.)	9.6 (8.96)	9.2 (12.22)	9.7 (11.26)
Minimum, maximum	0, 50	0, 99	0, 90
Baseline PEC score			
Mean (s.d.)	17.4 (1.80)	17.8	17.6 (2.06)
Baseline CGI-S			
Mean (s.d.)	3.9 (0.53)	4.0	4.1 (0.60)

Efficacy

PEC score

Primary

	Placebo n=115	Loxapine 5mg n=114	Loxapine 10mg n=110
Mean baseline	17.4	17.8	17.6
Change at 2 hours	-5.6	-7.6	-8.7
Difference from placebo	-	Not reported	-2.9 (-4.2, -1.6)
Change from baseline in PEC at 2 hours P value	-	0.0004	<0.0001

CGI-I score at 2 hours post dose

Secondary

	Placebo	Loxapine 5mg	Loxapine 10mg
Mean baseline CGI-S score	3.9	4.0	4.1
Mean CGI-I score	2.8	2.3	2.1
P value	-	0.0015	<0.0001

CGI-I responders

Analysis evaluated the percentage of subjects with scores of one (very much improved) or two (much improved) at 2 hours after Dose one. Both loxapine groups showed a significantly higher number of subjects judged to be very much improved or much improved compared to placebo (5mg: p=0.0015; 10mg: p <0.0001).

Time to second dose

A Kaplan-Meier survival analysis of the time to second dose showed an overall difference favoring the loxapine groups over placebo (p=0.0239). Individually the 10mg group showed significance to where the 5mg group did not (p=0.0076 and p=0.1155, respectively).

Safety	

	Placebo (n=115)	Loxapine 5mg (n=116)	Loxapine 10mg (n=113)
Subjects with an adverse event, n (%)	44 (38.3)	40 (34.5)	43 (38.1)
Dysgeusia	3 (2.6)	10 (8.6)	12 (10.6)
Dizziness	11 (9.6)	6 (5.2)	12 (10.6)
Sedation	11 (9.6)	15 (12.9)	12 (10.6)
Hypoaesthenia, oral	0	1 (0.9)	4 (3.5)
Headache	16 (13.9)	3 (2.6)	3 (2.7)
Somnolence	3 (2.6)	3 (2.6)	3 (2.7)
Nausea	6 (5.2)	1 (0.9)	2 (1.8)
Vomiting	3 (2.6)	1 (0.9)	1 (0.9)
Agitation	4 (3.5)	1 (0.9)	0

Overall inhaled loxapine was tolerated well. The percentage of subjects who had at least one adverse effect was similar to placebo. Most adverse effects were deemed mild or moderate and resolved with intervention.

The most common adverse effects seen were dysgeuisa, sedation and dizziness. Wheezing or bronchospasm was reported in three patients treated with inhaled loxapine. One subject in the 10mg group required albuterol to resolve the bronchospasm and withdrew from the study. Two subjects in the 5mg group reported wheezing but symptoms resolved without intervention.

Three severe adverse effects were reported in the 10mg group and the placebo group. In the 10mg group, one subject experienced concurrent severe adverse events of neck dystonia and oculogyration that determined to be treatment related, which were treated with benztropine and resolved. Another subject experienced severe sedation that was deemed to be due to treatment but resolved with no intervention. There was also a report of severe infectious gastroenteritis, which was ruled to be unrelated to treatment.

Conclusions	• Both groups assigned to inhaled loxapine, 5mg and 10mg, produced a significant improvement compared to placebo in the primary and key secondary endpoints. • Additional efficacy assessments provide additional support for the efficacy of inhaled loxapine in reducing agitation in people with schizophrenia. • Superior reduction in agitation as reflected by the PEC score were evident at the 10 minute assessment point compared to placebo. • Inhaled loxapine was tolerated well, with the most common adverse effects being known side effects of loxapine or minor oral effects common with inhaled medications. • No subjects refused treatment or were unable to take a dose of the study drug, which indicated easy use and potential for patient acceptance. • Overall this study supports that inhaled loxapine provides a rapid, effective and safe treatment option for individuals with agitation associated with schizophrenia.

Table 2. Acute treatment of agitation in patients with bipolar I disorder with inhaled loxapine

Citation	Kwentus J, Riesenberg R, Marandi M, Allen M, Fishman R, Spyker J et al. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. Bipolar Disord. 2012;14:31-40.
Study objective/purpose	Evaluate the efficacy and safety of inhaled loxapine for acute treatment of agitation with bipolar I disorder
Design	Phase III, multicentre, randomized, double-blind, placebo-controlled
Inclusion/Exclusion Criteria	**Inclusion** • 18-65 year old with bipolar I disorder, with either manic or mixed episodes (according to DSM-IV criteria, diagnosis confirmed prior to enrollment with the Mini International Neuropsychiatric Interview (MINI)) as applied by a research-trained psychiatrist on the basis of clinical presentation, psychiatric examination, known previously documented diagnosis when available, and history provided by a second source when available • Score of ≥ 14 (out of 35) and a score ≥ 4 (out of 7) on at least 1 of the 5 PEC items • Good general health as assessed by medical history, physical exam, 12-lead electrocardiogram, standard serum chemistry, hematology, and urinalysis • Nonpregnant and nonlactating females **Exclusion** • Agitation caused primarily by intoxication • Positive urine drug screen for psychostimulants • History of drug or alcohol dependence in past 2 months • Serious risk of suicide • Use of benzodiazepines or other hypnotics • Use of oral or short-acting IM antipsychotic drugs in the 4 hours before study treatment

	• Use of injectable depot neuroleptics within 1 dose interval before study treatment • Use of an investigational drug in the 30 days before screening • Clinically significant acute or chronic pulmonary disease • Clinically significant hepatic, renal, gastrenterologic, cardiovascular, endocrinologic, neurologic, or hematologic disease Continuation of ongoing and stable (unchanged for ≥ 7 days) doses of lithium or valproate was allowed, but initiation or dose adjustment of these agents during the trial was not allowed. Patients were not excluded based on extrapyramidal syndrome (EPS) or a history of EPS. Three of the 314 patients enrolled were taking benztropine at screening; none of these 3 received benztropine during the trial. One other patient received benztropine during the trial (as treatment for akathisia).
Exposure	Baseline assessments, which were conducted 30 minutes before study treatment, were the PEC scale, the Clinical Global Impression-Severity scale (a pre-treatment assessment of agitation), the Agitation-Calmness Evaluation Scale (ACES, a scale developed by Eli Lilly and Company) and vital sign measurements. Eligible patients were then randomized 1:1:1 to the following treatments: • 10mg of inhaled loxapine • 5mg of inhaled loxapine • Inhaled placebo After randomization, one dose was administered and the 24-hour observation period began. If necessary, a maximum of three doses of the study drug were allowed during the 24-hour period, if agitation did not subside sufficiently after dose one or recurred, dose two could be given > 2 hours after dose one; if necessary, dose three could be given > 4 hours after dose two. Rescue medication (IM lorazepam) was not allowed until after the 2 hour assessments had been completed, dose two had been given, and at least 20 minutes had elapsed after the last dose of study drug, unless deemed medically necessary. During the 24-hour observation period, participants were not to receive any other psychotropic drug that, in the opinion of the investigator, would confound study efficacy or safety end-point. Drugs prescribed to treat extrapyramidal symptoms were prohibited as well.
Endpoints	**Primary** • Mean change from baseline in the PEC score 2 hours after dose one of inhaled loxapine compared with the change from baseline after inhaled placebo **Secondary** • Absolute CGI-I score 2 hours after dose one of inhaled loxapine compared with inhaled placebo • Changes from baseline in the PEC scores at each assessment time from 10 minutes through to 24 hours after one dose • Analysis of CGI-I responders at 2 hours • Time to Dose #2

Results

314 patients were randomized and all received at least one dose of the study drug (loxapine or placebo) and 338 completed the study.

Patient demographics

	Placebo (n=105)	Loxapine 5mg (n=104)	Loxapine 10mg (n=105)
Age, years			
Mean (s.d)	40.6 (9.8)	41.2 (9.6)	40.5 (9.8)
Median	42.0	41.5	42.0
Minimum, maximum	19, 60	19, 62	19, 64
Gender, n (%)			
Female	49 (46.7)	57 (54.0)	52 (49.5)
Male	56 (53.3)	47 (45.2)	53 (50.5)
Ethnicity, n (%)			
White	33 (31.4)	58 (55.8)	47 (44.8)
Black	54 (41.4)	38 (36.5)	47 (44.8)
Hispanic	14 (13.3)	8 (7.7)	7 (6.7)
Asian	0	0	1 (1.0)
Native American	1 (1.0)	0	1 (1.0)
Other	0	0	1 (0.9)
Smoking history, n (%)			
Never smoked	17 (16.2)	20 (19.2)	18 (17.1)
Current smoker	78 (74.3)	79 (76.0)	77 (73.3)
Ex-smoker	10 (9.5)	5 (4.8)	10 (9.5)
Diagnosis, n (%)			
BD-I, manic episode	72 (68.6)	68 (72.4)	76 (72.4)
BD-I, mixed episode	33 (31.4)	36 (34.6)	29 (27.6)
Diagnosis, years			
Mean (s.d)	12.0 (10.1)	12.8 (8.9)	11.7 (9.1)
Minimum, maximum	0, 45	0, 38	0, 38
Duration of current agitation episode, days			
Mean (s.d.)	14.2 (21.5)	16.0 (32.4)	9.7 (10.2)
Minimum, maximum	0.25, 146	0.25, 210	0.25, 45
Number of previous hospitalizations			
Mean (s.d.)	5.86 (6.57)	5.54 (6.55)	5.06 (6.41)
Minimum, maximum	0, 30	0, 30	0, 30
Baseline PEC score			
Mean (s.d.)	17.7 (2.80)	17.4	17.3 (2.25)
Baseline CGI-S			
Mean (s.d.)	4.1 (0.57)	N/A	4.0 (0.49)

Efficacy

PEC score

Primary

	Placebo n=105	Loxapine 5mg n=104	Loxapine 10mg n=105
Mean baseline	17.7	17.4	17.3
Change at 2 hours	-4.7	-8.09	-9.2
Difference from placebo	-	-3.4	-4.5 (-5.8, -3.1)
Change from baseline in PEC at 2 hours P value	-	<0.0001	<0.0001

CGI-I score at 2 hours post dose

Secondary

	Placebo	Loxapine 5mg	Loxapine 10mg
Mean baseline CGI-S score	4.1	N/A	4.0
Mean CGI-I score	3.0	~ 2.1	1.9
P value	-	<0.0001	<0.0001

CGI-I responders

Analysis evaluated the percentage of subjects with scores of one (very much improved) or two (much improved) at 2 hours after dose one. Both loxapine groups showed a significantly higher amount of subjects were judged to be very much improved or much improved compared to placebo (5mg: p=0.0001, 10 mg: p <0.0001, respectively).

Time to second dose

A Kaplan-Meier survival analysis of the time to second dose showed an overall difference favoring the loxapine groups over placebo (p<0.0001). Individually both the 5mg and 10mg group showed statistical significance compared to placebo (p=0.0058 and p<0.0001, respectively).

Safety

	Placebo (n=105)	Loxapine 5mg (n=104)	Loxapine 10mg (n=105)
Subjects with an adverse event, n(%)	24 (22.9)	36 (34.6)	30 (28.6)
Diarrhea	3 (2.9)	1 (1.0)	0
Dizziness	8 (7.6)	6 (5.8)	5 (4.8)
Dysgeusia	6 (5.7)	18 (17.3)	18 (17.1)
Fatigue	3 (2.9)	4 (3.8)	2 (1.9)
Sedation	3 (2.9)	7 (6.7)	6 (5.7)
Headache	9 (8.6)	4 (3.8)	2 (1.9)
Stomach discomfort	2 (1.9)	3 (2.9)	1 (1.0)
Throat irritation	1 (1.0)	0	4 (3.8)

Overall inhaled loxapine was tolerated well. The percentage of subjects who had at least one adverse effect was similar to placebo. Most adverse effects were deemed mild or moderate and resolved with intervention.

The most common adverse effects seen were dysgeuisa, sedation and dizziness. There were no reports of wheezing, coughing or bronchospasm reported during the study.

Akathisia was reported in one patient in the 5mg loxapine group, which was deemed to be treatment related and was resolved after benztropine therapy. One patient in the 5mg loxapine group experienced moderate hypotension. There was also one report of hypertension in the loxapine 10mg group. Both of these incidences were resolved without intervention. There was one severe adverse effect of sedation in one patient treated with loxapine. Two patients in the 10mg loxapine group withdrew from the study due to moderate anxiety. There were no deaths reported in the study.

Conclusions

- Both groups of inhaled loxapine, 5mg and 10mg, produced a significant improvement compared to placebo in the primary and key secondary endpoints.
- Additional efficacy assessments provide additional support for the efficacy of inhaled loxapine in reducing agitation in patients with bipolar I disorder.
- Superior reduction in agitation as reflected by the PEC score, were evident at the 10 minute assessment point compared to placebo.
- Inhaled loxapine was tolerated well, with the most common adverse effects being know side effects of loxapine or minor oral effects common with inhaled medications.
- No subjects refused treatment or were unable to take a dose of the study drug, which indicated easy use and potential for patient acceptance.
- Overall this study supports that inhaled loxapine provides a rapid, effective and safe treatment option for individuals with agitation associated with bipolar disorder.

Appendix B: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.