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## Executive Summary

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EXECUTIVE SUMMARY

Background and epidemiology
Agitation associated with schizophrenia or bipolar I disorder is an acute behavioral emergency requiring immediate intervention. The Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V) defines “psychomotor agitation” as “excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still.” Agitation associated with schizophrenia or bipolar I disorder is also one of the most important contributors to the continued stigmatization of these mental illnesses.

Agitation presents as a continuum escalating through general anxiety, high anxiety, agitation, and aggression. Patients with agitation associated with schizophrenia or bipolar I disorder can escalate from showing signs of being distressed to exhibiting a loss of control. As the agitation intensifies, the ability of patients to cooperate can decrease, which may place the physician-patient therapeutic alliance in jeopardy.

Agitation associated with schizophrenia or bipolar I disorder:
• Schizophrenia and bipolar disorder are common causes of agitation among patients presenting in the emergency department
• Approximately 7 million episodes of agitation occur each year in the United States as a result of schizophrenia and bipolar I disorder
• Studies show that agitation was present in 30% to 82% of violent incidents by psychiatric patients

Impact of agitation associated with schizophrenia or bipolar I disorder
Agitation associated with schizophrenia or bipolar I disorder is not discussed nearly enough relative to its prevalence. When agitation presents, patients, caregivers, and medical staff, including nurses and physicians, may be impacted.
• Agitation associated with schizophrenia or bipolar I disorder is a personal, social, and economic burden that can escalate unpredictably and a warning signal that often precedes violence to others and self.\textsuperscript{1,6} Affected individuals are at risk of becoming aggressive and violent and of causing harm to themselves, others, and property. In fact, agitation is a leading cause of hospital staff injuries and a source of physical and psychological suffering for patients and others nearby.\textsuperscript{6}

• For patients with agitation associated with schizophrenia or bipolar I disorder, agitation can jeopardize relationships with caregivers.\textsuperscript{6,10,11} During an episode, patients want to be treated well and allowed to retain their dignity. In a survey conducted by Allen et al in 2003, psychiatric patients mentioned that being listened to about the kind of treatment they wanted, having someone contact their own doctor or therapist, and being given the medication they requested (because they know it has helped them in the past) were among the top strategies to help avoid restraint and seclusion during an episode.\textsuperscript{12}

• For caregivers, the impact of a patient’s agitation associated with schizophrenia or bipolar I disorder can trigger emotional reactions to the patient’s illness. In addition, this agitation or aggression can increase caregiver distress and hasten the need to hospitalize the agitated patient, which in turn increases the need for emergency room visits and has an adverse effect on the patient. In addition, the agitated patient and his or her family may face a substantial economic burden related to both support of the patient and to loss of overall family productivity.\textsuperscript{6}

• Nurses and physicians may become victims of assault when patients experience agitation associated with schizophrenia or bipolar I disorder that escalates into loss of control. An average of 8 assaults per year occur in the typical psychiatric emergency department (ED) due to agitation associated with schizophrenia or bipolar I disorder.\textsuperscript{6}

• Poorly managed agitation associated with schizophrenia or bipolar I disorder also presents a substantial economic burden to the healthcare system in both direct and indirect costs. Assaults on hospital staff result in lost work days, Workers’ Compensation claims, and treatment costs, among other expenses.\textsuperscript{5,11}

ADASUVE\textsuperscript{\textregistered} (loxapine) inhalation powder has not been demonstrated to affect these outcomes of agitation associated with schizophrenia or bipolar I disorder.

**Consensus recommendations for patients with agitation associated with schizophrenia or bipolar I disorder**

In 2001, the authors of the *Consensus Guidelines for Treatment of Behavioral Emergencies* recommended that the treatment goals for agitation associated with schizophrenia or bipolar I disorder should include\textsuperscript{1,2}:

• Rapid calming without oversedation

• No requirement of restraint

• Allow more accurate assessment of the underlying problem

• Participation by the patient

• Permit quicker discharge and/or disposition to appropriate setting

Patient, caregiver, and clinician statistics and perspectives surrounding the agitation behavioral emergency show that treatment should be offered quickly before dangerous behavior escalates.\textsuperscript{13} Treatments that allow for a patient’s involvement in selecting the medication are also the most useful and provide for a positive first impression; this, in turn, can affect future decisions positively.\textsuperscript{14}
ADASUVE® (loxapine) INHALATION POWDER

Indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults

ADASUVE was approved by the US Food and Drug Administration (FDA) in December 2012. It is administered via an inhaler and is the first and only FDA-approved treatment for agitation associated with schizophrenia or bipolar I disorder using this route of administration. ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD), or other pulmonary disease associated with bronchospasm.15

STACCATO® technology breath-actuated delivery system

STACCATO® technology is the inhalation delivery system for ADASUVE. It uses thermal vaporization that generates pure drug aerosols for alveolar deposition and uptake into the systemic circulation. Studies have shown that the STACCATO® system in the ADASUVE device delivers loxapine quickly with intravenous-like kinetics.16 In addition, unlike many inhalers that require a specific user technique and timing of actuation for efficient drug delivery, with the STACCATO® system patients need only take a steady deep breath and no hand-breath coordination is required.17

When a patient inhales, the STACCATO® system in the ADASUVE device vaporizes a thin film of excipient-free loxapine, providing rapid drug delivery.15,16 Studies have shown that the STACCATO® system delivers bioavailability of 9.1 mg of the 10 mg dose and that the variability of the important pharmacokinetic parameters (C_{max}, T_{max}, and AUC) through the inhalation route was comparable to intravenous delivery.16 Pharmacokinetic studies showed that inhaled loxapine has a median time to maximum plasma concentration of 2 minutes15; however, a correlation between pharmacokinetics and efficacy has not been established.
ADASUVE phase 3 clinical efficacy trials

Trial I included 344 patients who met Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) criteria for schizophrenia, and Trial II included 314 patients who met the DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features. The primary efficacy endpoint in both trials was the mean change from baseline in the total Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC) score, assessed 2 hours post dose. PEC is an investigator-rated instrument consisting of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. The key secondary endpoint was the mean Clinical Global Impression Improvement (CGI-I) Scale score at 2 hours. The CGI-I is an investigator-rated global assessment of symptom improvement, scored on a scale of 1 to 7. (See pages 37 and 38 for more information on PEC and CGI-I.)

ADASUVE met the primary endpoint in both trials, with statistical significance vs placebo (P<.0001). In both trials, rapid onset of action was demonstrated by a statistically significant decrease in agitation at 2 hours, with improvement apparent at 10 minutes following dosing and at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes post dose). ADASUVE achieved more than twice the effect of placebo in as early as 10 minutes in patients with schizophrenia or bipolar I disorder.15,18-21

Importantly, there were no apparent differences in response to treatment between subgroups based on age, gender, race, or baseline PEC score, or between patients with bipolar I disorder with manic or mixed episodes. All agitated patients in clinical trials, regardless of baseline PEC scores (ranging from 14 to 31 out of a possible 35), were able to use the device.21
**INDICATIONS AND USAGE**

ADASUVE® (loxapine) inhalation powder, for oral inhalation use, is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Efficacy was demonstrated in 2 trials in acute agitation: one in schizophrenia and one in bipolar I disorder.

**Limitations of Use:** As part of the ADASUVE Risk Evaluation and Mitigation Strategy (REMS) Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility.

**IMPORTANT SAFETY INFORMATION**

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**WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Bronchospasm**

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE.

Because of the risk of bronchospasm, ADASUVE 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. ADASUVE is not approved for the treatment of patients with dementia-related psychosis.

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- ADASUVE is contraindicated in patients with the following:
  - Current diagnosis or history of asthma, chronic obstructive pulmonary disease (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 ADASUVE treatment
  - Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine

- ADASUVE must be administered only by a healthcare professional

- Prior to administration, all patients must be screened for a history of pulmonary disease and examined (including chest auscultation) for respiratory abnormalities (e.g., wheezing)

- Administer only a single 10 mg dose of ADASUVE within a 24-hour period by oral inhalation using the single-use inhaler

- After ADASUVE administration, patients must be monitored for signs and symptoms of bronchospasm at least every 15 minutes for at least 1 hour

- ADASUVE can cause sedation, which can mask the symptoms of bronchospasm
Antipsychotic drugs can cause a potentially fatal symptom complex called Neuroleptic Malignant Syndrome (NMS), manifested by hyperpyrexia, muscle rigidity, altered mental state, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Associated features can include escalated serum creatine phosphokinase (CPK) concentration, rhabdomyolysis, elevated serum and urine myoglobin concentration, and renal failure. If NMS occurs, immediately discontinue antipsychotic drugs and other drugs that may contribute to the underlying disorder, monitor and treat symptoms, and treat any concomitant serious medical problems.

ADASUVE can cause hypotension, orthostatic hypotension, and syncope. Use with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that would predispose patients to hypotension. In the presence of severe hypotension requiring vasopressor therapy, epinephrine should not be used.

ADASUVE may increase the risk of falls, which could cause fractures or other injuries. Patients taking antipsychotics with certain health conditions or those on long-term therapy should be evaluated by their healthcare professional for the potential risk of falls.

Use ADASUVE with caution in patients with a history of seizures or with conditions that lower the seizure threshold. ADASUVE lowers the seizure threshold. Seizures have occurred in patients treated with oral loxapine and can also occur in epileptic patients.

Use caution when driving or operating machinery. ADASUVE can impair judgment, thinking, and motor skills.

The potential for cognitive and motor impairment is increased when ADASUVE is administered concurrently with other CNS depressants.

Treatment with antipsychotic drugs caused an increased incidence of stroke and transient ischemic attack in elderly patients with dementia-related psychosis; ADASUVE is not approved for the treatment of patients with dementia-related psychosis.

Use of ADASUVE may exacerbate glaucoma or cause urinary retention.

The most common adverse reactions (incidence ≥2% and greater than placebo) in clinical studies in patients with agitation treated with ADASUVE were dysgeusia, sedation, and throat irritation.

Pregnancy Category C. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk of extrapyramidal and/or withdrawal symptoms after delivery. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Discontinue drug or nursing, taking into account the importance of the drug to the mother.

The safety and effectiveness of ADASUVE in pediatric patients have not been established.
**Agitation associated with schizophrenia**¹⁵,¹⁸,²⁰

Individual patient PEC* scores in the schizophrenia trial ranged from 14 to 28 out of a possible 35. Mean baseline PEC scores in this trial were 17.4 for placebo and 17.6 for ADASUVE® (loxapine) inhalation powder.

The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with schizophrenia was established in a short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trial including 344 patients who met DSM-IV criteria for schizophrenia.

Patients receiving ADASUVE experienced:

- Statistically significant decreases (49% reduction) in agitation compared with placebo (33% reduction) at 2 hours post-dose (*P<.0001*)
- Nearly twice the effect of placebo at 10 minutes (*P<.0001*)
- Improvements following dosing at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes) (*P<.0001*)

---

*PEC* = Positive and Negative Syndrome Scale—Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme).
Agitation associated with bipolar I disorder\textsuperscript{15,19,21}

Individual patient PEC\textsuperscript{*} scores in the bipolar I disorder trial ranged from 14 to 31 out of a possible 35. Mean baseline PEC scores in this trial were 17.7 for placebo and 17.3 for ADASUVE\textsuperscript{®} (loxapine) inhalation powder.

The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with bipolar I disorder was established in a short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trial including 314 patients who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features.

Patients receiving ADASUVE experienced:

- Statistically significant decreases (53% reduction) in agitation compared with placebo (27% reduction) at 2 hours post-dose ($P<.0001$)
- More than twice the effect of placebo at 10 minutes ($P<.0001$)
- Improvements following dosing at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes) ($P<.0001$)

\textsuperscript{*}PEC=Positive and Negative Syndrome Scale-Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme).
Secondary endpoint in clinical trials
Patients receiving ADASUVE® (loxapine) inhalation powder experienced improvement in agitation as measured by the CGI vs placebo 2 hours post-dose ($P<.0001$).\(^\text{15}\)

**CGI-I score at 2 hours post-dose in SCHIZOPHRENIA and BIPOLAR I DISORDER trials\(^\text{15,18,19}\)**

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<thead>
<tr>
<th></th>
<th>SCHIZOPHRENIA</th>
<th></th>
<th>BIPOLAR I DISORDER</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n=115)</td>
<td>ADASUVE 10 mg (n=112)</td>
<td>Placebo (n=105)</td>
</tr>
<tr>
<td>Very Much Worse</td>
<td>7</td>
<td>2.8 $P&lt;.0001$</td>
<td>3.0 $P&lt;.0001$</td>
</tr>
<tr>
<td>Much Worse</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally Worse</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Change</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>3</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
<td>2</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>Very Much Improved</td>
<td>1</td>
<td></td>
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Adverse reactions in clinical trials
The safety profile of ADASUVE is based on data from the two 24-hour, randomized, double-blind, placebo-controlled, phase 3 clinical trials as well as 1 short-term, randomized, double-blind, placebo-controlled, phase 2 study. In the 3 trials, 259 patients received ADASUVE 10 mg and 263 received placebo.

The most common adverse reactions (incidence $\geq 2\%$ and greater than placebo) were dysgeusia, sedation, and throat irritation.

**Adverse reactions* in 3 short-term, placebo-controlled trials\(^\text{15}\)**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (n=263)</th>
<th>ADASUVE 10 mg (n=259)</th>
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<tbody>
<tr>
<td>Dysgeusia</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>Sedation</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0%</td>
<td>3%</td>
</tr>
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*These adverse reactions occurred at a rate of at least 2% in the ADASUVE 10 mg group and at a rate greater than in the placebo group.
Of all patients with agitation who received ADASUVE® (loxapine) inhalation powder 10 mg:

- Less than 1% experienced extrapyramidal symptoms (vs 0% with placebo)
  - One (0.4%) patient treated with ADASUVE developed neck dystonia and oculogyration, while the incidence of akathisia was 0.4% in patients treated with ADASUVE and 0% in patients treated with placebo
- Additionally, in a QTc study, ADASUVE did not prolong the QTc interval
  - In healthy adult subjects, the effect of ADASUVE on QTc prolongation was evaluated in a randomized, double-blinded, positive- (moxifloxacin 400 mg) and placebo-controlled parallel study

Symptoms of dystonia (prolonged abnormal contractions of muscle groups) may occur in susceptible individuals during treatment with ADASUVE. Acute dystonia tends to be dose related, but can occur at low doses, and occurs more frequently with first generation antipsychotics such as ADASUVE. The risk is greater in males and younger age groups.

Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope have been reported with oral administration of loxapine.

Patients with clinically significant acute or chronic pulmonary disease (eg, asthma, COPD, chronic bronchitis, and emphysema) were excluded from the trials. Smokers were not excluded from the clinical trials.

Airway adverse reactions in the trials:

- Bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred more frequently in patients (n=2/259) treated with ADASUVE 10 mg compared with patients (n=0/263) treated with placebo
- One patient with schizophrenia, without a history of pulmonary disease, had significant bronchospasm requiring rescue treatment with a bronchodilator and oxygen
- ADASUVE can cause sedation, which can mask the symptoms of bronchospasm

### Pulmonary safety studies in subjects without psychiatric disease

Three studies were designed and conducted to assess pulmonary safety in healthy volunteers and in subjects with asthma or COPD with no psychiatric history. The effect of ADASUVE on pulmonary function was evaluated in 3 randomized, double-blind, placebo-controlled, pulmonary safety studies:

- Healthy volunteers (N=30); 2-way crossover
- Subjects with asthma (N=52)
- Subjects with COPD (N=53)

The primary outcome measure of these studies was the change in FEV₁ from baseline.

- FEV₁ (forced expiratory volume) is a lung test that is measured during spirometry that measures how much air a person can exhale during a forced breath. FEV₁ measures the amount of air exhaled in 1 second

The studies were designed to assess safety in subjects with asthma or COPD with no psychiatric history. Results from the studies showed:

- There were no lasting effects from any adverse events through the end of the study period (34 hours)
- No serious adverse events were reported
- Clinical pulmonary safety trials demonstrated that ADASUVE can cause bronchospasm as measured by FEV₁, and as indicated by respiratory signs and symptoms in the trials
ADASUVE® (loxapine) inhalation powder is contraindicated in patients with a history of asthma, COPD, or other lung disease associated with bronchospasm.

**Healthy volunteers**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=26)</th>
<th>ADASUVE 10 mg (n=26)</th>
</tr>
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<tbody>
<tr>
<td>Maximum FEV$_1$ decrease ≥20% after Dose 1</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Maximum FEV$_1$ decrease ≥20% after Dose 2</td>
<td>0%</td>
<td>4%</td>
</tr>
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- In this crossover study, 30 volunteers (26 evaluable for FEV$_1$ assessment) received 2 doses of either ADASUVE or placebo 8 hours apart, and 2 doses of the alternate treatment at least 4 days later.
- No volunteers in this trial developed airway-related adverse reactions (cough, wheezing, chest tightness, or dyspnea).

**Subjects with asthma**

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<thead>
<tr>
<th></th>
<th>Placebo (n=26)</th>
<th>ADASUVE 10 mg (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum FEV$_1$ decrease ≥20% after Dose 1</td>
<td>4%</td>
<td>23%</td>
</tr>
<tr>
<td>Maximum FEV$_1$ decrease ≥20% after Dose 2</td>
<td>4%</td>
<td>30%</td>
</tr>
<tr>
<td>Subjects with respiratory adverse reactions</td>
<td>12%</td>
<td>54%</td>
</tr>
<tr>
<td>Rescue medication (albuterol) required</td>
<td>12%</td>
<td>54%</td>
</tr>
</tbody>
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- 52 subjects with mild-moderate persistent asthma (with FEV$_1$ ≥60% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose.
A second dose of study medication was not administered to 9/26 (35%) subjects treated with ADASUVE® (loxapine) inhalation powder and 1/26 (4%) subjects treated with placebo because they had a ≥20% decrease in FEV₁ or they developed respiratory symptoms after the first dose.

Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat tightness, and wheezing) occurred in 54% of subjects treated with ADASUVE and 12% of subjects treated with placebo.

Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 54% of subjects (7 subjects [27%] after the first dose and 7 of the remaining 17 subjects [41%] after the second dose) treated with ADASUVE and 12% of subjects treated with placebo (1 subject after the first dose and 2 subjects after the second dose).

As shown above, there was a marked decrease in FEV₁ immediately following the first dose (maximum mean decreases in FEV₁ and % predicted FEV₁ were 303 mL and 9.1%, respectively). Furthermore, the effect on FEV₁ was greater following the second dose (maximum mean decreases in FEV₁ and percentage predicted FEV₁ were 537 mL and 14.7%, respectively).
• 53 subjects with mild to severe COPD (with FEV₁ ≥40% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose.
  – 57% had moderate COPD, 32% had severe COPD, and 11% had mild COPD

• A second dose of study medication was not administered to 7/25 (28%) subjects treated with ADASUVE and 1/27 (4%) subjects treated with placebo because they had a ≥20% decrease in FEV₁ or they developed respiratory symptoms after the first dose

• Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat tightness, and wheezing) occurred in 19% of subjects treated with ADASUVE and 11% of subjects treated with placebo

• Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 23% of subjects (8% after the first dose and 21% after the second dose) treated with ADASUVE and 15% of subjects treated with placebo

### ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)
Because of the risk of bronchospasm that can lead to respiratory distress and respiratory arrest, ADASUVE has Boxed Warnings, is available only through a restricted program under a REMS, and must be administered only in an enrolled healthcare facility by a healthcare professional. Required components of the ADASUVE REMS are that healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements and certified healthcare facilities must have immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (eg, albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm. Wholesalers and ADASUVE distributors must distribute only to enrolled healthcare facilities. Further information is available at ADASUVEREMS.COM or 855-755-0492.
ADASUVE® (loxapine) inhalation powder is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm or those with acute respiratory symptoms or signs (such as wheezing). It is also contraindicated in patients taking medications used to treat airways disease and those with a history of bronchospasm following ADASUVE treatment in the past.

In addition, elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, and ADASUVE is not approved for the treatment of patients with dementia-related psychosis. ADASUVE has not been studied in elderly patients (>65 years of age).

Prior to administering ADASUVE, clinicians must screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD, and other lung disease associated with bronchospasm, and ask patients about current use of medications to treat airways disease (such as asthma or COPD), and examine patients (including chest auscultation) for respiratory abnormalities. They must monitor patients for symptoms or signs of bronchospasm after ADASUVE administration. As part of the examination, chest auscultation should be performed at least every 15 minutes for at least 1 hour after ADASUVE administration. Healthcare professionals must also monitor patients for signs and symptoms of bronchospasm following treatment with ADASUVE.

**A therapeutic option in the treatment of agitation associated with schizophrenia or bipolar I disorder**¹⁵,¹⁸-²¹

ADASUVE is a therapeutic option for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. ADASUVE, the first and only orally inhaled drug indicated for agitation associated with schizophrenia or bipolar I disorder, combines a rapid onset of action with oral inhalation administration. Whereas physicians previously had to choose between IM injections and oral medications to treat patients with agitation associated with schizophrenia or bipolar I disorder, ADASUVE provides a treatment option that offers rapid onset via oral inhalation.
SECTION I

Definition and description of agitation associated with schizophrenia or bipolar I disorder

Epidemiology and burden of agitation associated with schizophrenia or bipolar I disorder

Warning signs and risk factors
Definition and description of agitation associated with schizophrenia or bipolar I disorder

Psychomotor agitation is defined by the *DSM-V* as “Excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still.”

Patients who experience agitation associated with schizophrenia or bipolar I disorder describe feeling an inner distress (nervous, restless, overwhelmed, out of control, anguish, panic) that can progress to an outwardly apparent loss of control manifested by cursing, hostility, and difficulty controlling impulses, with uncooperative behavior and increased potential for violence. The time course for escalation of agitation associated with schizophrenia or bipolar I disorder is unpredictable.

Patients experiencing agitation often manifest behaviors that interfere with their care. Common features of agitation associated with schizophrenia or bipolar I disorder include excessive motor and/or verbal activity, irritability, uncooperativeness, vocal outbursts or abuse, threatening gestures or language, physical destruction, and assault. Agitation is a warning signal that often precedes violence to others and self.

It is a behavioral syndrome characterized by motor restlessness, heightened responsiveness to internal and external stimuli, and inappropriate verbal or motor activity.

### Continuum of agitation severity

![Continuum of agitation severity](image)

*Primary clinical endpoint: Positive and Negative Syndrome Scale-Excited Component (PEC).

Epidemiology and burden of agitation associated with schizophrenia or bipolar I disorder

Much of the existing epidemiologic data on agitation are derived from patient visits in the psychiatric emergency setting, where agitation has been described as a “common symptom” among emergency patients with schizophrenia or bipolar I disorder. However, experts believe that agitation associated with schizophrenia or bipolar I disorder is usually underreported and underdiscussed. It is estimated that 2.7 million and 6.5 million people live with schizophrenia or bipolar disorder respectively. Those with schizophrenia will experience an average of 12 episodes of agitation per year (5 in the medical setting), while those with bipolar I disorder will also experience 12 episodes per year (2 in a medical setting). This adds up to approximately 7 million episodes of agitation associated with schizophrenia or bipolar I disorder in the medical setting per year.

Prevalence numbers were calculated using National Institute of Mental Health percentages (cited) and 2016 census data from the United States Census Bureau.
In addition:

- Agitation is present in 30% to 82% of violent incidents by psychiatric patients.

- Nursing staff are especially vulnerable. Six times as many nurses as physicians are assaulted by agitated patients.
  - Every year 10% of inpatient psychiatric nurses experience an injury as a result of patient aggression.
  - In the ED, the 2010 Emergency Nurses Association Study found that half of ED nurses reported verbal or physical threats within the prior 7 days.

**Burden of agitation associated with schizophrenia or bipolar I disorder**

Agitation associated with schizophrenia or bipolar I disorder also presents a financial burden to the healthcare system in regard to both direct and indirect costs. The annual cost of conflict and containment measures (e.g., verbal aggression, uncooperative behavior, special observation, seclusion, restraints) in psychiatric units in the United States was estimated at $455 million in 2010. Importantly, these estimates do not include the cost of agitation in general EDs, extended lengths of hospital stays that have been associated with agitation in psychiatric patients, and many other direct and indirect costs.

ADASUVE® (loxapine) inhalation powder has not been demonstrated to affect these outcomes of agitation associated with schizophrenia or bipolar I disorder.

**Warning signs and risk factors**

While agitation associated with schizophrenia or bipolar I disorder is distinct from physical aggression, warning signs of agitation often proceed rapidly to aggressive and violent behavior. Given that physical restraint and seclusion are high-risk measures of last resort for agitated patients with schizophrenia or bipolar I disorder, identifying aggressive behavior in at-risk patients may allow for early, focused treatment and the ability to avoid restraint or seclusion.

Specific behavioral warning signs and cues precede most violent episodes. These include:

- Explosive or unpredictable anger
- Intimidation
- Restlessness
- Pacing
- Excessive movement
- Physical or verbal self-abuse
- Verbally demeaning or hostile behavior
- Uncooperative or demanding behavior
- Impulsiveness and impatience
### SECTION 2

- Treatment guidelines for patients with agitation associated with schizophrenia or bipolar I disorder
- Nonpharmacologic interventions should be attempted first
- Rationale for use of medication in patients with agitation associated with schizophrenia or bipolar I disorder
- Consensus statement on agitation associated with schizophrenia or bipolar I disorder treatment protocol
- Current treatment options for patients with agitation associated with schizophrenia or bipolar I disorder
- Rationale for ADASUVE® (loxapine) inhalation powder
Treatment guidelines for patients with agitation associated with schizophrenia or bipolar I disorder

Because poorly managed agitation often results in the inappropriate use of coercive measures or escalates to patient violence, consensus guidelines have been developed regarding the use and avoidance of seclusion and restraint. This emphasis on avoidance of coercion and restraints is shared by the Health Care Financing Administration (HCFA) for facilities receiving Medicare and Medicaid payments and The Joint Commission (TJC). Both of these agencies have developed and endorsed specific regulations on those topics. They consider low rates of restraint a key healthcare quality indicator.\(^{25}\)

A noncoercive approach is currently recommended as the standard of care for treatment of patients with agitation associated with schizophrenia or bipolar I disorder.\(^{1}\) The goal of this approach is to calm the patient and gain his or her cooperation in evaluation and treatment of the agitation in order to avoid the negative outcomes associated with the use of forced medication, seclusion, and restraint.\(^{1,14}\)

To help achieve these goals, Consensus Guidelines recommend\(^{1,25}\):

- Exclude medical etiologies for symptoms
- Provide rapid stabilization of the acute crisis
- Avoid coercion
- Treat in the least restrictive setting
- Form a therapeutic alliance
- Provide appropriate disposition and after-care plan

Nonpharmacologic interventions should be attempted first

Consensus Guidelines recommend that patients with agitation associated with schizophrenia or bipolar I disorder be immediately treated upon recognition of initial cues, starting with nonpharmacological interventions to de-escalate the agitation.\(^{1}\)

Effective de-escalation includes:\(^{1}\):

- Paying particular attention to volume, tone, and rate of speech
- Listening more than speaking
- Respecting the patient’s personal space
- Employing nonthreatening body language
- Setting limits
Rationale for use of medication in patients with agitation associated with schizophrenia or bipolar I disorder

When initial verbal methods have failed to calm a patient, medication is often part of de-escalation techniques and pharmacotherapy is frequently an essential part of reducing agitation.\(^1\) The primary goal of using medication is to rapidly calm the patient, so that he or she can be more accurately assessed by clinicians.\(^1,14\)

Among the rationale given was a study by the National Emergency Department that documented agitation associated with a variety of psychiatric conditions. In this study, at least 25% of ED staff feel safe at work “sometimes,” “rarely,” or “never”; they also cited the 2010 Emergency Nurses Association study, which reported that more than half of ED nurses had been verbally or physically threatened at work within the past 7 days. Agitation can also be dangerous for patients, as agitation associated with schizophrenia or bipolar I disorder escalating to violence and even death has been reported.\(^1,14\)

For psychosis-driven agitation such as in patients with schizophrenia or bipolar I disorder, medications that target the underlying etiology (antipsychotics) are often used. In addition, patients should be involved in the process of selecting medication to whatever extent possible (eg, oral vs IM).\(^14\)

General treatment recommendations for agitation associated with schizophrenia or bipolar I disorder\(^14\)

1. The use of medication as a restraint (ie, to restrict movement) should be discouraged. Rather, clinicians should, to whatever extent possible, attempt a provisional diagnosis of the most likely cause of the agitation and target medication to the most likely disease.

2. Nonpharmacologic approaches, such as verbal de-escalation and reducing environmental stimulation (quiet room, low lighting), should be attempted, if possible, before medications are administered.

3. Medication should be used to calm patients.

4. Patients should be involved in the process of selecting medication to whatever extent possible (eg, oral vs IM).

5. If the patient is able to cooperate with taking oral medications, consider these over IM preparations.
Consensus statement on agitation associated with schizophrenia or bipolar I disorder treatment protocol

Based on a consensus statement of the American Association for Emergency Psychiatry Project BETA psychopharmacology workgroup

The figure to the right outlines a step-wise approach for care of the patient with agitation associated with schizophrenia or bipolar I disorder. There is no type of medication considered to be “best” in all cases of agitation, but 3 general classes of medication have been studied and used most frequently for agitation: first-generation antipsychotics, second-generation antipsychotics, and benzodiazepines. Three routes of administration are possible: conventional oral tablets or orally disintegrating tablets (ODTs), intramuscular injections (IMs), or intravenous (IV). For psychosis-driven agitation associated with schizophrenia or bipolar I disorder, antipsychotics address the underlying psychosis. Clinical data support the use of second-generation antipsychotics in the treatment of acute agitation, either alone or with an adjunctive medication. If the patient is willing to accept oral medication, oral antipsychotics may be used. If the patient cannot cooperate with oral medications, IM antipsychotics are preferred for acute control of agitation. If an initial dose of antipsychotic is insufficient to control agitation, the addition of a benzodiazepine should be considered.

Since the publication of these guidelines in 2012, there have been further developments in pharmacologic approaches that include inhaled, buccal/sublingual and intranasal formulations which “although requiring cooperation from patients, should be used whenever possible to improve overall patient experience, thereby potentially improving future cooperation between patients and healthcare providers. At the time of this publication, inhaled loxapine is the only non-injectable option specifically approved by the FDA for this purpose.”

The table summarizes information about route of administration and onset of effect for different treatment options indicated for patients presenting with agitation associated with schizophrenia or bipolar I disorder in the United States.\textsuperscript{1,27}

No published adequate and well-controlled head-to-head studies have been conducted between ADASUVE and any current marketed competitor therapy. This table should not be construed to suggest that comparisons could be made between ADASUVE and the therapies in the table.

### Treatment goals for agitation associated with schizophrenia or bipolar I disorder\textsuperscript{1,14}

- Rapid calming without oversedation
- No requirement of restraint
- Allow more accurate assessment of the underlying problem
- Facilitate participation by patient in their care
- Permit quicker discharge and/or disposition to appropriate setting
Rationale for ADASUVE® (loxapine) inhalation powder

ADASUVE is a first-generation antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. It is the first and only orally inhaled medicine indicated for agitation associated with schizophrenia or bipolar I disorder. ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other pulmonary disease associated with bronchospasm.15

In clinical trials, ADASUVE provided statistically significant reductions in agitation at 2 hours, with improvement rapidly achieved at 10 minutes following dosing.15

Reduction from baseline in agitation symptoms18,19

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SCHIZOPHRENIA</th>
<th>BIPOLAR I DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADASUVE 10 mg (n=112)</td>
<td>Placebo (n=115)</td>
</tr>
<tr>
<td>At 2 hours (primary)</td>
<td>49%</td>
<td>33%</td>
</tr>
<tr>
<td>At 10 minutes (secondary)</td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>

PEC=Positive and Negative Syndrome Scale-Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme). Mean baseline total PEC score was 17.3 to 17.7.

In both trials, the primary efficacy endpoint was the mean change from baseline PEC score, assessed 2 hours after dosing.
Due to the risk of bronchospasm, ADASUVE® (loxapine) inhalation powder is available only through a restricted REMS program and must be administered only in an enrolled healthcare facility.15

**ADASUVE is breath actuated.** Hand-breath coordination or forceful inhalation are not required during ADASUVE administration.15

- ADASUVE is a single-use, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine
- STACCATO® technology vaporizes pure loxapine to form an aerosol that is quickly absorbed through the lungs and into the bloodstream16
- Oral inhalation through the device initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally-generated drug vapor. The vapor condenses into aerosol particles that are dispersed into the airstream created by the patient inhaling through the mouthpiece

*Please see Important Safety Information on page 54, including Boxed Warnings.*
ADASUVE® (loxapine) inhalation powder

Indications and usage

Description

Clinical pharmacology

STACCATO® technology breath-actuated delivery system

Clinical trials

Baseline characteristics

Trial I—Acute treatment of agitation in patients with schizophrenia

Trial II—Acute treatment of agitation in patients with bipolar I disorder

Clinical trials adverse reactions

Pulmonary safety studies in subjects without psychiatric disease

Pulmonary safety summary

Boxed Warnings, REMS, Contraindications and Warnings, and Precautions

Increased mortality in elderly patients with dementia-related psychosis

Dosage and administration

Monitoring to assess safety

Drug interactions

Use in specific populations

Special populations

Overdosage

Nonclinical toxicology

How supplied

References
**Indications and usage**

ADASUVE® (loxapine) inhalation powder, for oral inhalation use, is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

“Psychomotor agitation” is defined in *DSM-V* as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their care (eg, threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior), leading clinicians to the use of rapidly absorbed antipsychotic medications to achieve immediate control of the agitation.

The efficacy of ADASUVE was established in one study of acute agitation in patients with schizophrenia and one study of acute agitation in patients with bipolar I disorder.

**Limitations of Use**

As part of the ADASUVE REMS Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility.

**Description**

ADASUVE, a typical antipsychotic, is an inhalation powder of loxapine supplied in a single-use, disposable inhaler containing 10 mg of loxapine base. ADASUVE is a drug-device combination product.

**Active Ingredient:** Loxapine (base). Loxapine, a dibenzoxazepine compound, represents a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Chemically, it is 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine.

ADASUVE is a single-use, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally-generated drug vapor. The vapor condenses into aerosol particles that are dispersed into the airstream created by the patient inhaling through the mouthpiece.

Each product is packaged inside a sealed foil pouch. The product is a white to off-white plastic unit, with a mouthpiece on one end and a pull-tab protruding from the other end.

Removal of a pull-tab from the product renders it ready for use, as indicated by illumination of a green light. After inhalation through the mouthpiece, successful dosing is signaled by the green light turning off. Under standardized *in vitro* test conditions, ADASUVE 10 mg delivers 9.1 mg of loxapine out of the mouthpiece.

**Clinical pharmacology**

**Background**

Typical antipsychotics or first-generation antipsychotics have a long history of use for the treatment of agitation. The exact mechanism of calming with first-generation antipsychotics is unknown but most likely due to their inhibition of dopamine transmission in the human brain, which reduces the underlying psychotic symptoms causing the agitation.
Mechanism of action of loxapine

The mechanism of action of loxapine in the treatment of agitation associated with schizophrenia is unknown. However, its efficacy could be mediated through a combination of antagonism of central dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors. The mechanism of action of loxapine in the treatment of agitation associated with bipolar I disorder is unknown.

Pharmacodynamics

Loxapine acts as an antagonist at central serotonin and dopamine receptors, with high affinity for serotonin 5-HT<sub>2A</sub> and dopamine D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors (K<sub>i</sub> values of 2 nM, 18 nM, 10 nM, 21 nM, 9 nM, respectively). Some of the adverse effects of loxapine may be related to the antagonism of histamine H<sub>1</sub> (somnolence), muscarinic M1 (anticholinergic), and adrenergic α<sub>2</sub> (orthostatic hypotension) receptors (K<sub>i</sub> values of 15 nM, 117 nM, and 250 nM, respectively).

Thorough QTc study

ADASUVE<sup>®</sup> (loxapine) inhalation powder did not prolong the QTc interval. The effect of ADASUVE on QTc prolongation was evaluated in a randomized, double-blinded, positive- (moxifloxacin 400 mg) and placebo-controlled parallel study in healthy subjects. A total of 48 healthy subjects were administered ADASUVE 10 mg. In this study with a demonstrated ability to detect small effects, the upper bound of the 90% confidence interval (CI) for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method was below 10 milliseconds, the threshold for regulatory concern.

Pharmacokinetics

Absorption

The single-dose pharmacokinetic parameters of loxapine following administration of single doses of ADASUVE 10 mg in healthy adult subjects are presented in the table and figure below. Administration of ADASUVE resulted in rapid absorption of loxapine, with a median time of maximum plasma concentration (T<sub>max</sub>) of 2 minutes. Loxapine exposure in the first 2 hours after administration (AUC<sub>0-2h</sub>) was 66.7 ng·h/mL for the 10 mg dose.

As a consequence of the very rapid absorption of loxapine after oral inhalation, there is substantial variability in the early plasma concentrations of loxapine. The mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical dose range. AUC<sub>0-2h</sub>, AUC<sub>inf</sub> and C<sub>max</sub> increased in a dose-dependent manner.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy subjects ADASUVE 10 mg (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-2h&lt;/sub&gt; (ng·h/mL), mean ± SD</td>
<td>66.7 ± 18.2</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt; (ng·h/mL), mean ± SD</td>
<td>188 ± 47</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL), mean ± SD</td>
<td>257 ± 219</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (minutes), median (25%, 75%)</td>
<td>1.13 (1, 2)</td>
</tr>
<tr>
<td>Half-life (hours), mean ± SD</td>
<td>7.61 ± 1.87</td>
</tr>
</tbody>
</table>
Mean plasma concentrations of loxapine in healthy subjects following single-dose administration of ADASUVE® (loxapine) inhalation powder 10 mg\textsuperscript{15}

- Administration of ADASUVE resulted in rapid absorption of loxapine, with a median time of maximum plasma concentration ($T_{\text{max}}$) of 2 minutes

Pharmacokinetics in smokers
The half-life of ADASUVE is 7.6 hours and loxapine exposures (pharmacokinetics) in nonsmokers and smokers are similar. No dosage adjustment is recommended based on smoking status.

ADASUVE is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other pulmonary disease associated with bronchospasm.

Demographic effects
There were no clinically significant differences in loxapine pharmacokinetics following administration of ADASUVE in subgroups based on age, weight, body mass index, gender, or race.
Distribution

Loxapine is removed rapidly from the plasma and distributed in tissues. Animal studies following oral administration suggest an initial preferential distribution in the lungs, brain, spleen, heart, and kidney. Loxapine is 96.6% bound to human plasma proteins.

Metabolism

Loxapine is metabolized extensively in the liver following oral administration, with multiple metabolites formed. The main metabolic pathways include: (1) hydroxylation to form 8-OH-loxapine by CYP1A2 and 7-OH-loxapine by CYP3A4 and CYP2D6, (2) N-oxidation to form loxapine N-oxide by flavanoid monoamine oxidases (FMOs), and (3) de-methylation to form amoxapine. Because there are multiple metabolic pathways, the risk of metabolic interactions caused by an effect on an individual isoform is minimal. For ADASUVE® (loxapine) inhalation powder, the order of metabolites observed in humans (based on systemic exposure) was 8-OH-loxapine >> loxapine N-oxide, 7-OH-loxapine > amoxapine. Plasma levels of 8-OH-loxapine are similar to those of the parent compound.

Excretion

Excretion occurs mainly in the first 24 hours. Metabolites are excreted in the urine in the form of conjugates and in the feces unconjugated. The terminal elimination half-life ($T_{1/2}$) ranged from 6 to 8 hours.

Transporter interaction

*In vitro* studies indicated that loxapine was not a substrate for p-glycoprotein (P-gp); however, loxapine inhibited P-gp.

**STACCATO® technology breath-actuated delivery system**

**Background**

STACCATO® technology is the inhalation delivery system for ADASUVE. It uses thermal vaporization that generates pure drug aerosols for alveolar deposition and uptake into the systemic circulation. Studies have shown that the STACCATO® system in the ADASUVE device delivers loxapine quickly and with intravenous-like kinetics. In addition, unlike inhalers that require a specific user technique and timing of actuation for efficient drug delivery, with the STACCATO® system patients need only take a steady deep breath and no hand-breath coordination is required.

**Studies show the consistency of STACCATO® technology**

*In vitro* product characterization experiments show that loxapine delivered by STACCATO® technology consistently performs for the emitted dose, aerosol purity, and particle size distribution over a wide range of scenarios. Exposure of the ADASUVE device to mechanical shock, drops, vibration, thermal cycling, light exposure, and flow rates did not alter performance, and use in different ambient temperatures, humidity levels, altitudes, and product orientations showed consistency.

Two in vivo clinical studies have been conducted in which the pharmacokinetics of aerosols from the STACCATO® system were evaluated in crossover dosing with an intravenous administration of the same drug. Both studies showed that the STACCATO® system delivered bioavailability of nearly 100% of the emitted dose and that the variability of the important pharmacokinetic parameters ($C_{\text{max}}$, $T_{\text{max}}$, and AUC) through the inhalation route was comparable to the intravenous delivery. It is not known how pharmacology correlates to clinical efficacy or safety results.
How STACCATO® technology works

When the patient inhales, the STACCATO® system in the ADASUVE® (loxapine) inhalation powder device vaporizes excipient-free loxapine to form a condensation aerosol (via the rapid heating of a thin film of loxapine) to enable rapid drug delivery. As the patient inhales through the mouthpiece, a thermal pulse causes the film of loxapine to quickly vaporize and then condense into the airstream to produce aerosol particles (see image below).16,17

The STACCATO® system in the ADASUVE device15-17

The STACCATO® system consists of 3 core components: a heating substrate, a thin film of loxapine on the substrate, and a mouthpiece where the aerosol forms and is dispersed into the inhaled airstream. The substrate’s surface transiently reaches temperatures of approximately 400°C within approximately 200 milliseconds after being triggered by a patient’s inhalation, before cooling quickly back to room temperature. This thermal pulse causes the drug film to vaporize quickly and then condense in the airstream to produce aerosol particles.16,17
**STACCATO® technology delivers loxapine in a single breath**\(^{16,17}\)

The STACCATO® system in the ADASUVE® (loxapine) inhalation powder device actuates at a specific threshold flow rate regardless of ramp-up time. Most of the aerosol is generated and emitted in the first 500 milliseconds for delivery into the lungs.\(^2\) The loxapine aerosol does not contain excipients, or require priming, hand-breath coordination, or forceful inhalation. The aerosol is dispersed into the airstream during the patient’s inhalation.

**Clinical trials**

**Psychometric scales used in the clinical trials**

Evaluation for agitation associated with schizophrenia or bipolar I disorder in the ADASUVE clinical trials was based on the following validated psychiatric rating instruments\(^{15}\):

- Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)
- Clinical Global Impression Improvement (CGI-I) Scale

**Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)**

PEC is an investigator-rated instrument consisting of 5 items\(^{15}\):

- Poor impulse control
- Tension
- Hostility
- Uncooperativeness
- Excitement

Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme). Although the total PEC score ranges from 5 to 35, patients in the clinical trials had to have a PEC score of ≥14, with at least one individual item score >4. Total scores can range from 5 (all symptoms absent) to 35 (all symptoms extreme). In the pivotal phase 3 clinical trials for agitation associated with both schizophrenia and bipolar I disorder, patients were evaluated at 10, 20, 30, and 45 minutes, and at 1, 1.5, 2, 4, and 24 hours after treatment. The primary endpoint was the change from baseline PEC score at 2 hours after dosing with ADASUVE or placebo. Baseline was measured 30 minutes before treatment with ADASUVE.\(^{15,18,19}\)
Clinical Global Impression Severity (CGI-S) Scale
The CGI-S was used in the clinical trials as a pretreatment assessment of agitation severity 30 minutes before treatment with ADASUVE® (loxapine) inhalation powder was initiated. The CGI-S is an investigator-rated assessment with scores that could range from 1 (normal) to 7 (extreme agitation).15,19,20

Clinical Global Impression Improvement (CGI-I) Scale
The CGI-I was the key secondary endpoint of both trials and was taken at 2 hours post-dosing with ADASUVE or placebo. The CGI-I is an investigator-rated global assessment of symptom improvement from baseline measurement with the CGI-S. The CGI-I was scored on a scale 1 (very much improved) to 7 (very much worse).15

Trial design15
The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with schizophrenia or bipolar I disorder was established in 2 short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial I</td>
<td>344 patients who met the DSM-IV criteria for schizophrenia and was conducted at 24 psychiatric research facilities throughout the United States between February and June of 2008.15,18,20</td>
</tr>
<tr>
<td>Trial II</td>
<td>314 patients who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features, and was conducted at 17 psychiatric research facilities throughout the United States between July and November of 2008.15,19,21</td>
</tr>
</tbody>
</table>

In both trials, the primary efficacy endpoint was the mean change from baseline in the total PEC score, assessed 2 hours after dosing. The key secondary endpoint was the mean CGI-I score at 2 hours. Additional endpoints included the changes from baseline in the PEC scores at different time points between 10 minutes and 2 hours. Safety was evaluated by treatment-emergent adverse events (AEs), vital signs, physical exams, and laboratory tests.15,20,21
Male and female patients aged 18 to 65 years were drawn from the following settings:\textsuperscript{20,21}:

- Individuals admitted to a hospital setting or research unit in order to be enrolled
- Already hospitalized patients with schizophrenia who had agitation
- Individuals treated at a psychiatric ED that permitted extended patient stays in secluded observation for the duration of the study

At baseline, in the 30 minutes before study treatment, agitation was reconfirmed using the PEC score and the patient was further assessed with the CGI-S score and by taking vital signs. Following randomization, the first dose of study medication or placebo was administered and the 24-hour evaluation period began. A total of 3 doses of medication could be administered within the 24-hour study period if agitation did not subside or recurred (second dose >2 hours after first dose and third dose ≥4 hours after second dose). Lorazepam IM rescue was allowed only after the second dose of study medication was given.\textsuperscript{18,19}

During the trial, agitation was assessed by the PEC score at 10, 20, 30, and 45 minutes, and at 1, 1.5, 2, 4, and 24 hours after the first dose and by the CGI-I score at 2 hours after the first dose.\textsuperscript{15,18-21}

\textbf{Phase 3 clinical trial design}
Patients were enrolled in the trials if they met the criteria below.

**Inclusion and exclusion criteria**[^20][^21]

<table>
<thead>
<tr>
<th>Trial I</th>
<th>Acute agitation associated with SCHIZOPHRENIA</th>
<th>Trial II</th>
<th>Acute agitation associated with BIPOLAR I DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td></td>
<td><strong>Inclusion criteria</strong></td>
<td></td>
</tr>
<tr>
<td>• Schizophrenia (according to <strong>DSM-IV</strong> 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</td>
<td>• Agitated patients with bipolar I disorder, with either manic or mixed episodes (according to <strong>DSM-IV</strong> criteria, diagnosis confirmed prior to enrollment with the Mini International Neuropsychiatric Interview [MINI])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Score ≥14 (out of 35) and a score ≥4 (out of 7) on at least 1 of the 5 PEC items</td>
<td>• Score ≥14 (out of 35) and a score ≥4 (out of 7) on at least 1 of the 5 PEC items</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Good general health as assessed by medical history, physical exam, 12-lead electrocardiogram, standard serum chemistry, hematology, and urinalysis</td>
<td>• Good general health as assessed by medical history, physical exam, 12-lead electrocardiogram, standard serum chemistry, hematology, and urinalysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nonpregnant and nonlactating females</td>
<td>• Nonpregnant and nonlactating females</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exclusion criteria**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Agitation caused primarily by intoxication</td>
<td>• Agitation caused primarily by intoxication</td>
<td></td>
</tr>
<tr>
<td>• Positive urine drug screen for psychostimulants</td>
<td>• Positive urine drug screen for psychostimulants</td>
<td></td>
</tr>
<tr>
<td>• History of drug or alcohol dependence in past 2 months</td>
<td>• History of drug or alcohol dependence in previous 2 months</td>
<td></td>
</tr>
<tr>
<td>• Serious risk of suicide</td>
<td>• Serious risk of suicide</td>
<td></td>
</tr>
<tr>
<td>• Use of benzodiazepines or other hypnotics</td>
<td>• Use of benzodiazepines or other hypnotics</td>
<td></td>
</tr>
<tr>
<td>• Use of oral or short-acting IM antipsychotic drugs in the 4 hours before study treatment</td>
<td>• Use of oral or short-acting IM antipsychotic drugs in the 4 hours before study treatment</td>
<td></td>
</tr>
<tr>
<td>• Use of injectable depot neuroleptics within 1 dose interval before study treatment</td>
<td>• Use of injectable depot neuroleptics within 1 dose interval before study treatment</td>
<td></td>
</tr>
<tr>
<td>• Use of an investigational drug in the 30 days before screening</td>
<td>• Use of an investigational drug in the 30 days before screening</td>
<td></td>
</tr>
<tr>
<td>• Clinically significant acute or chronic pulmonary disease</td>
<td>• Clinically significant acute or chronic pulmonary disease</td>
<td></td>
</tr>
<tr>
<td>• Clinically significant hepatic, renal, gastroenterologic, cardiovascular, endocrinologic, neurologic, or hematologic disease</td>
<td>• Clinically significant hepatic, renal, gastroenterologic, cardiovascular, endocrinologic, neurologic, or hematologic disease</td>
<td></td>
</tr>
</tbody>
</table>

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 benztrpine at screening; none of these 3 received benztrpine during the trial. One other patient received benztrpine during the trial (as treatment for akathisia).

[^20]: Reference 20
[^21]: Reference 21
Patient characteristics
The phase 3 trials enrolled agitated patients with either schizophrenia or bipolar I disorder who presented to trial sites through normal channels by which psychiatric patients obtain treatment for agitation.20,21 The patients had sufficient levels of agitation at baseline to warrant treatment and to assess the efficacy and safety of ADASUVE® (loxapine) inhalation powder. They also had significant and long-standing psychiatric disease, based on years since diagnosis.18,19 For patients with schizophrenia, the mean time since diagnosis ranged from 16.5 to 18.8 years and at screening, the mean duration of the current episode of agitation ranged from 6.1 to 7.6 days.18 For patients with bipolar I disorder, the mean time since diagnosis ranged from 11.7 to 12.8 years and at screening, the mean duration of the current episode of agitation ranged from 9.7 to 16.0 days (medians ranged from 5.0 to 6.2 days).19 These findings demonstrate that the phase 3 program included patients who were significantly agitated and representative of the patient population requiring treatment of agitation in clinical practice.

Baseline characteristics
Demographics
In both phase 3 trials, the treatment groups were generally well matched with respect to demographic characteristics.18-21

**Demographic characteristics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>SCHIZOPHRENIA</th>
<th>BIPOLAR I DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=115)</td>
<td>ADASUVE 10 mg (n=113)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>80 (69.6)</td>
<td>86 (76.1)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>43.9 (9.45)</td>
<td>42.2 (9.82)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>32 (27.8)</td>
<td>36 (31.9)</td>
</tr>
<tr>
<td>Black</td>
<td>70 (60.9)</td>
<td>67 (59.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (7.8)</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3.5)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>90 (78.3)</td>
<td>97 (85.8)</td>
</tr>
</tbody>
</table>
Psychiatric history

Agitation at baseline was similar in both phase 3 trials and across all treatment groups. Patients in both trials had significant and long-standing psychiatric disease. At screening, the duration of the current episode of agitation for patients with schizophrenia was, on average, 7.6 days for patients randomized to ADASUVE® (loxapine) inhalation powder 10 mg and 9.7 days for those with bipolar I disorder.\textsuperscript{18,19}

**Psychiatric history\textsuperscript{18-21}**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>SCHIZOPHRENIA</th>
<th>BIPOLAR I DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=115)</td>
<td>ADASUVE 10 mg (n=113)</td>
</tr>
<tr>
<td>Time since diagnosis, mean years (SD)</td>
<td>18.8 (10.34)</td>
<td>18.2 (10.03)</td>
</tr>
<tr>
<td>Baseline PEC score, mean (SD)</td>
<td>17.4 (1.80)</td>
<td>17.6 (2.06)</td>
</tr>
<tr>
<td>Baseline CGI-S, mean (SD)</td>
<td>3.9 (0.53)</td>
<td>4.1 (0.60)</td>
</tr>
</tbody>
</table>
Efficacy

Patients receiving ADASUVE® (loxapine) inhalation powder met the primary efficacy endpoint in both trials with statistical significance.15,18,19

- In both trials, mean baseline PEC scores were similar in all treatment groups, averaging 17.3 for ADASUVE to 17.7 for placebo15
- Individual patient scores ranged from 14 to 31 out of a possible 35, indicating predominantly moderate levels of agitation15
- In both trials, treatment with ADASUVE was statistically significantly superior to placebo for the mean change in PEC score at 2 hours (P<.0001)15,18,19
### SCHIZOPHRENIA

<table>
<thead>
<tr>
<th>PEC score</th>
<th>Placebo</th>
<th>ADASUVE® (loxapine) inhalation powder 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>17.4</td>
<td>17.6</td>
</tr>
<tr>
<td>Change at 2 hours*</td>
<td>–5.8</td>
<td>–8.7</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)†</td>
<td>—</td>
<td>–2.9 (–4.2, –1.6)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>—</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

### BIPOLAR I DISORDER

<table>
<thead>
<tr>
<th>PEC score</th>
<th>Placebo</th>
<th>ADASUVE® (loxapine) inhalation powder 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>17.7</td>
<td>17.3</td>
</tr>
<tr>
<td>Change at 2 hours*</td>
<td>–4.7</td>
<td>–9.2</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)†</td>
<td>—</td>
<td>–4.5 (–5.8, –3.1) (n=105)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>—</td>
<td>&lt;.0001 (n=105)</td>
</tr>
</tbody>
</table>

*Least squares mean for the difference defined as the change from baseline.

†Least squares mean for the difference defined as the change from baseline at hour 2 in the drug group minus that in the placebo group.
**Primary endpoint**

The chart below shows the mean change in total PEC\(^*\) score over time. The primary endpoint was the change from baseline PEC score at 2 hours after dosing with ADASUVE\(^{®}\) (loxapine) inhalation powder or placebo. Baseline was measured 30 minutes before treatment with ADASUVE. Treatment with ADASUVE 10 mg was superior to placebo at 2 hours. The differences can be seen with ADASUVE starting at 10 minutes after treatment and continuing to all subsequent assessments throughout the 24-hour period ($P<$0.0001). 39\% of the total effect with ADASUVE was observed at 10 minutes, representing a 20\% reduction from baseline.

Individual patient PEC scores in the schizophrenia trial ranged from 14 to 28 out of a possible 35. Mean baseline PEC scores in this trial were 17.4 for placebo and 17.6 for ADASUVE.

**SCHIZOPHRENIA**  Mean change from baseline in PEC score through 2 hours after a single dose

**PEC** = Positive and Negative Syndrome Scale-Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderately, 7=extreme).

The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with schizophrenia was established in a short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trial including 344 patients who met DSM-IV criteria for schizophrenia.
Patients receiving ADASUVE® (loxapine) inhalation powder experienced:

- Statistically significant decreases (49% reduction) in agitation compared with placebo (33% reduction) at 2 hours post-dose ($P<.0001$)
- Nearly twice the effect of placebo at 10 minutes ($P<.0001$)
- Improvements following dosing at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes) ($P<.0001$)

In addition, there were no notable differences in response to treatment with ADASUVE between subgroups based on age, gender, race, or agitation level at baseline.\textsuperscript{26}

**Secondary endpoints**

Patients receiving ADASUVE met the key secondary endpoint of CGI-I at 2 hours after initiation of treatment. The mean CGI-I score was 2.1 vs 2.8 for placebo; $P<.0001$.

### CGI-I score at 2 hours post-dose

<table>
<thead>
<tr>
<th>SCHIZOPHRENIA</th>
<th>Placebo (n=115)</th>
<th>ADASUVE 10 mg (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Much Worse</td>
<td>7</td>
<td>ADASUVE 10 mg (n=112)</td>
</tr>
<tr>
<td>Much Worse</td>
<td>6</td>
<td>2.1</td>
</tr>
<tr>
<td>Minimally Worse</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>No Change</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Minimally Improved</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Much Improved</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Very Much Improved</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

$P<.0001$
**Trial II**  
**Acute treatment of agitation in patients with bipolar I disorder**[^15,19,21]

**Primary endpoint**

The chart below shows the mean change in total PEC* score over time. The primary endpoint was the change from baseline PEC score at 2 hours after dosing with ADASUVE® (loxapine) inhalation powder or placebo. Baseline was measured 30 minutes before treatment with ADASUVE. The differences compared with placebo can be seen with ADASUVE starting at 10 minutes after treatment and continuing to all subsequent assessments throughout the 24-hour period ($P<.0001$). 43% of the total effect with ADASUVE was observed at 10 minutes, representing a 23% reduction from baseline.

Individual patient PEC scores in the bipolar I disorder trial ranged from 14 to 31 out of a possible 35. Mean baseline PEC scores in this trial were 17.7 for placebo and 17.3 for ADASUVE.

---

**BIPOLAR I DISORDER**  
**Mean change from baseline in PEC score through 2 hours after a single dose**

<table>
<thead>
<tr>
<th>Time After Treatment</th>
<th>10 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (n=105)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADASUVE 10 mg (n=105)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PEC=Positive and Negative Syndrome Scale-Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme).

The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with bipolar I disorder was established in a short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trial including 314 patients who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features.
Patients receiving ADASUVE® (loxapine) inhalation powder experienced:

- Statistically significant decreases (53% reduction) in agitation compared with placebo (27% reduction) at 2 hours post-dose ($P<.0001$)
- More than twice the effect of placebo at 10 minutes ($P<.0001$)
- Improvements following dosing at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes) ($P<.0001$)

In addition, there were no notable differences in response to treatment with ADASUVE between subgroups based on age, gender, race, or agitation level at baseline.\textsuperscript{26}

Secondary endpoints

Patients receiving ADASUVE met the key secondary endpoint of CGI-I at 2 hours after initiation of treatment. The mean CGI-I score was 3.0 for placebo and 1.9 for ADASUVE; $P<.0001$.

Clinical trials adverse reactions\textsuperscript{15}

The safety profile of ADASUVE is based on pooled data from the two 24-hour, randomized, double-blind, placebo-controlled, phase 3 clinical trials described above as well as 1 short-term, randomized, double-blind, placebo-controlled, phase 2 study. In the 3 trials, 259 patients received ADASUVE 10 mg and 263 received placebo.

The most common adverse reactions (incidence ≥2% and greater than placebo) were dysgeusia, sedation, and throat irritation. Specifically, 14% of patients taking ADASUVE 10 mg compared with 5% of patients taking placebo experienced dysgeusia; 12% of patients taking ADASUVE 10 mg compared with 10% of patients taking placebo reported sedation; and 3% of patients taking ADASUVE 10 mg compared with 0% of patients taking placebo reported throat irritation.
These adverse reactions occurred at a rate of at least 2% in the ADASUVE 10 mg group and at a rate greater than in the placebo group.

Of all patients with agitation who received ADASUVE 10 mg:

- Less than 1% experienced extrapyramidal symptoms (vs 0% with placebo)
- One (0.4%) patient treated with ADASUVE developed neck dystonia and oculogyration, while the incidence of akathisia was 0.4% in patients treated with ADASUVE 10 mg and 0% in patients treated with placebo
- Additionally, in a thorough QTc study, ADASUVE did not prolong the QTc interval
  - In healthy adult subjects, the effect of ADASUVE on QTc prolongation was evaluated in a randomized, double-blinded, positive- (moxifloxacin 400 mg) and placebo-controlled parallel study

Symptoms of dystonia (prolonged abnormal contractions of muscle groups) may occur in susceptible individuals during treatment with ADASUVE. Acute dystonia tends to be dose related, but can occur at low doses and occurs more frequently with first-generation antipsychotics such as ADASUVE. The risk is greater in males and younger age groups.\(^{15}\)

Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope have been reported with oral administration of loxapine.\(^{15}\)

Patients with clinically significant acute or chronic pulmonary disease (eg, clinically apparent asthma, bronchitis, emphysema) were excluded from the phase 2 and phase 3 clinical trials. Smokers were not excluded from the clinical trials.\(^{15,18,19}\)

### Airway adverse reactions in the trials

- Bronchospasm (which includes reports of wheezing, shortness of breath, and cough) occurred more frequently in patients (n=2/259) treated with ADASUVE 10 mg compared with patients (n=0/263) treated with placebo\(^{15}\)
- One patient with schizophrenia, without a history of pulmonary disease, had significant bronchospasm requiring rescue treatment with a bronchodilator and oxygen\(^{15}\)
- ADASUVE can cause sedation, which can mask the symptoms of bronchospasm\(^{15}\)

### Adverse reactions* in 3 short-term, placebo-controlled trials\(^{15}\)

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (n=263)</th>
<th>ADASUVE (loxapine) inhalation powder 10 mg (n=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>Sedation</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*These adverse reactions occurred at a rate of at least 2% in the ADASUVE 10 mg group and at a rate greater than in the placebo group.
Pulmonary safety studies in subjects without psychiatric disease

Three studies were designed and conducted to assess pulmonary safety in healthy volunteers and in subjects with asthma or COPD with no psychiatric history. The effect of ADASUVE® (loxapine) inhalation powder on pulmonary function was evaluated in 3 randomized, double-blind, placebo-controlled, pulmonary safety studies in:

- Healthy volunteers (N=30); 2-way crossover
- Subjects with asthma (N=52)
- Subjects with COPD (N=53)

The primary outcome measure of these studies was the change in FEV₁ from baseline.

- FEV₁ (forced expiratory volume) is a lung test that is measured during spirometry that measures how much air a person can exhale during a forced breath. FEV₁ measures the amount of air exhaled in 1 second.

The studies were designed to assess safety in subjects with asthma or COPD with no psychiatric history. Results from the studies showed:

- There were no lasting effects from any adverse events through the end of the study period (34 hours)
- No serious adverse events were reported

ADASUVE is contraindicated in patients with a history of asthma, COPD, or other lung disease associated with bronchospasm.

Healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=26)</th>
<th>ADASUVE 10 mg (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum FEV₁ decrease ≥20% after Dose 1</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Maximum FEV₁ decrease ≥20% after Dose 2</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- In this crossover study, 30 volunteers (26 evaluable for FEV₁ assessment) received 2 doses of either ADASUVE or placebo 8 hours apart and 2 doses of the alternate treatment at least 4 days later
- No volunteers in this trial developed airway-related adverse reactions (cough, wheezing, chest tightness, or dyspnea)
52 subjects with mild-moderate persistent asthma (FEV₁ ≥60% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose.

A second dose of study medication was not administered to 9/26 (35%) subjects treated with ADASUVE and 1/26 (4%) subjects treated with placebo because they had a ≥20% decrease in FEV₁ or they developed respiratory symptoms after the first dose.

Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat, tightness, and wheezing) occurred in 54% of subjects treated with ADASUVE and 12% of subjects treated with placebo.

Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 54% of subjects treated with ADASUVE (7 patients (27%) after the first dose and 7 of the remaining 17 subjects (41%) after the second dose) and 12% of subjects treated with placebo (1 patient after the first dose and 2 patients after the second dose).
As shown above, there was a marked decrease in FEV₁ immediately following the first dose (maximum mean decreases in FEV₁ and % predicted FEV₁ were 303 mL and 9.1%, respectively). Furthermore, the effect on FEV₁ was greater following the second dose (maximum mean decreases in FEV₁ and % predicted FEV₁ were 537 mL and 14.7%, respectively). 

*LS mean=least squares mean.
Subjects with COPD\textsuperscript{15}

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=27)</th>
<th>ADASUVE\textsuperscript{®} (loxapine) inhalation powder 10 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum FEV(_1) decrease ≥20% after Dose 1</td>
<td>7%</td>
<td>36%</td>
</tr>
<tr>
<td>Maximum FEV(_1) decrease ≥20% after Dose 2</td>
<td>4%</td>
<td>26%</td>
</tr>
<tr>
<td>Subjects with respiratory adverse reactions</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Rescue medication (albuterol) required</td>
<td>15%</td>
<td>23%</td>
</tr>
</tbody>
</table>

- 53 subjects with mild to severe COPD (with FEV\(_1\) ≥40% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose
  - 57% had moderate COPD, 32% had severe COPD, and 11% had mild COPD
- A second dose of study medication was not administered to 7/25 (28%) subjects treated with ADASUVE and 1/27 (4%) subjects treated with placebo because they had a ≥20% decrease in FEV\(_1\) or they developed respiratory symptoms after the first dose
- Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat, tightness, and wheezing) occurred in 19% of subjects treated with ADASUVE and 11% of subjects treated with placebo
- Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 23% of subjects (8% after the first dose and 21% after the second dose) treated with ADASUVE and 15% of subjects treated with placebo

Pulmonary safety summary

In all pulmonary safety studies, bronchospasm was identified as a safety concern. Clinical pulmonary safety trials demonstrated that ADASUVE can cause bronchospasm as measured by FEV\(_1\), and as indicated by respiratory signs and symptoms in the trials. Airway adverse events were mild to moderate and common in patients with active airways disease. Airway adverse events were managed with an inhaled bronchodilator, and there was a quick response to inhaled albuterol in which bronchospasm was manageable and reversible.

The PLACID study

The PLACID study was a phase 3b trial that evaluated the efficacy and safety of ADASUVE compared with IM aripiprazole for the treatment of acute agitation in patients with schizophrenia and bipolar I disorder.\textsuperscript{29}
Boxed Warnings, REMS, Contraindications, and Warnings and Precautions

**WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Bronchospasm**

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (eg, albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE.

Because of the risk of bronchospasm, ADASUVE 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. ADASUVE is not approved for the treatment of patients with dementia-related psychosis.

The product labeling for ADASUVE includes Boxed Warnings for bronchospasm and increased mortality in elderly patients with dementia-related psychosis. It states that:

- ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest
- Prior to administering ADASUVE, clinicians must screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD, and other lung disease associated with bronchospasm, and ask patients about current use of medications to treat airways disease (such as asthma or COPD). They must examine patients for acute respiratory symptoms or signs. As part of the examination, chest auscultation must be performed
- Healthcare professionals also must monitor patients for signs and symptoms of bronchospasm following treatment with ADASUVE
- Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS
- It can only be administered in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (eg, albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm
- ADASUVE is contraindicated in patients with a current diagnosis of asthma, COPD or other lung disease associated with bronchospasm or those with acute respiratory symptoms or signs (such as wheezing). It is also contraindicated in patients taking medications used to treat airways disease and those with a history of bronchospasm following ADASUVE treatment in the past
- In addition, elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, and ADASUVE is not approved for the treatment of patients with dementia-related psychosis. ADASUVE has not been studied in elderly patients

Patients should also be monitored for signs and symptoms of bronchospasm after ADASUVE administration. It is recommended that physicians perform a physical examination, including chest auscultation, at least every 15 minutes for at least 1 hour after administration of ADASUVE.
Risk Evaluation and Mitigation Strategy (REMS)\(^{15}\)

Due to the risk of bronchospasm, ADASUVE\(^\circledast\) (loxapine) inhalation powder is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS. This requires that ADASUVE be administered only in an enrolled healthcare facility by a healthcare professional. Required components of the ADASUVE REMS are:

- Healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (eg, albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.

- Wholesalers and distributors that distribute ADASUVE must distribute only to enrolled healthcare facilities.

Further information is available at ADASUVEREMS.COM or 855-755-0492.

Contraindications\(^{15}\)

ADASUVE is contraindicated in patients with the following:

- Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm
- Acute respiratory symptoms or signs (eg, wheezing)
- Current use of medications to treat airways disease, such as asthma or COPD
- History of bronchospasm following ADASUVE treatment
- Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine

Bronchospasm\(^{15}\)

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. ADASUVE should only be administered in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services. Facilities must have a short-acting bronchodilator (eg, albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history of asthma, COPD, and other lung disease associated with bronchospasm, acute respiratory symptoms or signs, current use of medications to treat airways disease, such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities (eg, wheezing). Monitor patients for symptoms and signs of bronchospasm (ie, vital signs and chest auscultation) at least every 15 minutes for a minimum of 1 hour following treatment with ADASUVE. ADASUVE can cause sedation, which can mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm, as indicated by changes in forced expiratory volume in 1 second (FEV\(_1\)), was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose within a 24-hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE.
Increased mortality in elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared with a rate of about 2.6% in the placebo group. Although the cases of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies can be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ADASUVE® (loxapine) inhalation powder is not approved for the treatment of elderly patients with dementia-related psychosis.

In addition to the warnings described above, the following warnings and precautions should be considered:

1. **Neuroleptic Malignant Syndrome (NMS):** May develop in patients treated with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

2. **Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease, or conditions that would predispose patients 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 beta stimulation may worsen hypotension in the setting of ADASUVE-induced partial alpha blockade.

3. **Risk of Falls:** ADASUVE may increase the risk of falls, which could cause fractures or other injuries. Patients taking antipsychotics with certain health conditions or those on long-term therapy should be evaluated by their healthcare professional for the potential risk of falls.

4. **Seizure:** ADASUVE lowers the seizure threshold. Use with caution in patients with a history of seizures or with conditions that lower the seizure threshold. In short-term (24-hour), placebo-controlled trials of ADASUVE, there were no reports of seizures.

5. **Potential for Cognitive and Motor Impairment:** Use caution when driving or operating machinery. ADASUVE can impair judgment, thinking, and motor skills. In short-term, placebo-controlled trials, sedation and/or somnolence were reported in 12% and 10% in the ADASUVE and placebo groups, respectively. No patients discontinued treatment because of sedation or somnolence. The potential for cognitive and motor impairment is increased when ADASUVE is administered concurrently with other CNS depressants. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ADASUVE does not affect them adversely.

6. **Cerebrovascular Adverse Reactions:** In placebo-controlled trials with atypical antipsychotics in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse reactions (stroke and transient ischemic attacks), including fatalities, compared with placebo-treated patients. ADASUVE is not approved for the treatment of patients with dementia-related psychosis.

7. **Anticholinergic Reactions:** ADASUVE has anticholinergic activity, and it has the potential to cause anticholinergic adverse reactions including exacerbation of glaucoma or urinary retention. The concomitant use of other anticholinergic drugs (e.g., antiparkinson drugs) with ADASUVE could have additive effects.
Dosage and administration

ADASUVE® (loxapine) inhalation powder must be administered only by a healthcare professional. ADASUVE is administered by oral inhalation only. The recommended dose for acute agitation is 10 mg administered by oral inhalation using a single-use inhaler. Only a single dose within a 24-hour period should be administered.

Required examination prior to dosing

Prior to administering ADASUVE, all patients should be screened for a history of asthma, COPD, or other pulmonary disease, and examined (including chest auscultation) for respiratory signs (eg, wheezing).

Important administration instructions

**Step 1. Open the pouch**
When ready to use, tear open the foil pouch and remove the inhaler from the package. When the ADASUVE inhaler is removed from the pouch, the indicator light is off.

**Step 2. Pull tab**
Firmly pull the plastic tab from the rear of the inhaler. Check that the green light turns on. This indicates that the inhaler is ready for use. Use the inhaler within 15 minutes after removing the tab to prevent automatic deactivation of the inhaler. The green light will turn off indicating that the inhaler is not usable. Discard the inhaler after 1 use.

**Step 3. Explain procedures to the patient**
Explain the administration procedures to the patient prior to use and advise the patient that it is important to follow the instructions. Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.

**Step 4. Instruct the patient to exhale**
Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs.

**Step 5. Instruct the patient to inhale**
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 the green light turns off indicating that the dose has been delivered.

**Step 6. Instruct the patient to hold breath**
Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds. Important: If the green light remains on after the patient inhales, the dose of ADASUVE 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.

See page 35 for a description of the ADASUVE breath-actuated device.
Monitoring to assess safety\textsuperscript{15}

After administration of ADASUVE\textsuperscript{®} (loxapine) inhalation powder, patients should be monitored for signs and symptoms of bronchospasm. Physicians should perform a physical examination, including chest auscultation, at least every 15 minutes for at least 1 hour after ADASUVE administration.

Drug interactions\textsuperscript{15}

CNS depressants

Because ADASUVE is a central nervous system (CNS) depressant, the concurrent use of ADASUVE with other CNS depressants (eg, alcohol, opioid analgesics, benzodiazepines, tricyclic antidepressants, general anesthetics, phenothiazines, sedative/hypnotics, muscle relaxants, and/or illicit CNS depressants) can increase the risk of respiratory depression, hypotension, profound sedation, and syncope. Physicians should consider reducing the dose of CNS depressants if used concomitantly with ADASUVE.

Anticholinergic drugs

ADASUVE has anticholinergic activity. The concomitant use of ADASUVE and other anticholinergic drugs can increase the risk of anticholinergic adverse reactions including exacerbation of glaucoma and urinary retention.

Use in specific populations\textsuperscript{15}

Pregnancy Category C

Risk summary

There are no adequate and well-controlled studies of ADASUVE use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. 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/m\textsuperscript{2} basis. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

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

Animal data

In rats, embryofetal toxicity (increased fetal resorptions, reduced weights, and hydronephrosis with hydroureter) was observed following oral administration of loxapine during the period of organogenesis at a dose of 1 mg/kg/day. This dose is equivalent to the MRHD of 10 mg/day on a mg/m\textsuperscript{2} basis. In addition, fetal toxicity (increased prenatal death, decreased postnatal survival, reduced fetal weights, delayed ossification, and/or distended renal pelvis with reduced or absent papillae) was observed following oral administration of loxapine from mid-pregnancy through weaning at doses of 0.6 mg/kg and higher. This dose is approximately half the MRHD of 10 mg/day on a mg/m\textsuperscript{2} basis.
No teratogenicity was observed following oral administration of loxapine during the period of organogenesis in the rat, rabbit, or dog at doses up to 12, 60, and 10 mg/kg, respectively. These doses are approximately 12-, 120-, and 32-fold the MRHD of 10 mg/day on a mg/m² basis, respectively.

**Nursing mothers**

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

**Pediatric use**

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

**Geriatric use**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of dementia-related psychosis. Placebo-controlled studies of ADASUVE in patients with agitation associated with schizophrenia or bipolar I disorder did not include patients over 65 years of age.

**Special populations**

**Pharmacokinetics in smokers:** Loxapine exposures in nonsmokers and smokers are similar, with geometric mean ratios of 92%, 85%, and 99% for AUC_{0-2h}, AUC_{inf}, and C_{max}, respectively. No dosage adjustment is recommended based on smoking status.

**Demographic effects:** There were no clinically significant differences in loxapine pharmacokinetics following administration.

**Overdosage**

**Signs and symptoms of overdosage**

As would be expected from the pharmacologic actions of loxapine, the clinical findings may include CNS depression, unconsciousness, profound hypotension, respiratory depression, extrapyramidal symptoms, and seizure.

**Management of overdosage**

For the most up to date information on the management of ADASUVE overdosage, contact a certified poison control center (1-800-222-1222 or www.poison.org). Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.
Nonclinical toxicology

Carcinogenesis: No adequate studies have been conducted.

Mutagenesis: Loxapine did not cause mutation or chromosomal aberration when tested in vitro and in vivo. Loxapine was negative in the Ames gene mutation assay, the human peripheral blood lymphocyte chromosomal aberration assay, and in the in vivo mouse bone marrow micronucleus assay up to 40 mg/kg (20-fold the MRHD on mg/m² basis).

Loxapine metabolite 8-OH-loxapine was not mutagenic in the in vitro Ames reverse mutation assay and was not clastogenic in the in vitro human peripheral blood lymphocyte chromosomal aberration assay.

Impairment of fertility: Loxapine had no effects on fertility or early embryonic development in male rats or in male and female rabbits following oral administration. Mating was decreased in female rats because these animals were in persistent diestrus, an expected pharmacologic effect for this class of compounds. This occurred at doses approximately 0.2- and 1-fold the MRHD of 10 mg/day on a mg/m² basis.

Animal toxicology and/or pharmacology

In the rat, minimal and reversible squamous metaplasia of the larynx was observed after daily inhalation exposure of loxapine for 14 days at 1.7 to 13 mg/kg/day (approximately 2- to 13-fold the MRHD of 10 mg/day on a mg/m² basis, respectively). This finding was considered a nonspecific particle impaction effect. Mammary hyperplasia in males and females and ovarian follicular cysts and mucification of vaginal epithelium in female rats were observed at all doses, with partial or complete recovery at the end of 14 days of treatment. In the dog, no effects on the respiratory tract or reproductive tissues were observed after inhalation exposure to loxapine for 28 days at doses up to 1.8 mg/kg/day (approximately 6-fold the MRHD of 10 mg/day on a mg/m² basis).

How supplied

ADASUVE® (loxapine) inhalation powder 10 mg (NDC 10885-003-01) is a single-use, disposable inhaler containing 10 mg of loxapine, provided in a sealed foil pouch. ADASUVE 10 mg is supplied in a carton of 5 units per carton (NDC 10885-003-05).

Storage and handling

Store ADASUVE at room temperature, 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep out of reach of children and in pouch until time of use. ADASUVE contains a lithium battery. Dispose of ADASUVE in accordance with all federal, state, and local laws.
References


WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Bronchospasm

- ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest (4, 5.1)
- ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS (5.2)
- Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. Facilities must have a short-acting bronchodilator, including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm (5.1, 5.2)

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. ADASUVE is not approved for the treatment of patients with dementia-related psychosis (5.3)

**RECENT MAJOR CHANGES**

Boxed Warning 9/2016
Warnings and Precautions (5.1, 5.2) 9/2016
Warnings and Precautions (5.6) 1/2017

**INDICATIONS AND USAGE**

ADASUVE is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Efficacy was demonstrated in 2 trials in acute agitation: one in schizophrenia and one in bipolar I disorder (1, 14)

Limitations of Use:
ADASUVE must be administered only in an enrolled healthcare facility (1)

**DOSE AND ADMINISTRATION**

- Must be administered only by a healthcare professional (2.1)
- 10 mg by oral inhalation using an inhaler (2.1)
- Administer only a single dose within any 24-hour period (2.1)
- Prior to administering, screen all patients for a history of pulmonary disease, and examine patients (including chest auscultation) for respiratory abnormalities (e.g. wheezing) (2.2)
- Refer to Full Prescribing Information for important instructions on use of the ADASUVE inhaler (2.3)
- After administration, monitor patients for signs and symptoms of bronchospasm at least every 15 minutes for at least one hour (2.4)
- Inhalation powder: 10 mg unit in a single-use inhaler (3)

**CONTRAINDICATIONS**

- Current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm (4)
- Acute respiratory signs/symptoms (e.g., wheezing) (4)
- Current use of medications to treat airways disease, such as asthma or COPD (4)
- History of bronchospasm following ADASUVE treatment (4)
- Known hypersensitivity to loxapine or amoxapine (4)

**WARNINGS AND PRECAUTIONS**

- Neuroleptic Malignant Syndrome: May develop in patients treated with antipsychotic drugs. Discontinue treatment (5.4)
- Hypotension and Syncope: Use with caution in patients with known cardiovascular or cerebrovascular disease (5.5)
- Seizure: Use with caution in patients with a history of seizures or with conditions that lower the seizure threshold (5.7)
- Potential for Cognitive and Motor Impairment: Use caution when driving or operating machinery (5.8)
- Cerebrovascular Adverse Reactions: Increased incidence of stroke and transient ischemic attack in elderly patients with dementia-related psychosis treated with antipsychotic drugs (5.9)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence ≥ 2% and greater than placebo) were dysgeusia, sedation, and throat irritation (6.1)

To report SUSPECTED ADVERSE REACTIONS contact Galen US Inc. at 1-800-284-0062 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised 08/2017
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
   16.1 How Supplied
   16.2 Restricted Access
   16.3 Storage and Handling
17 PATIENT COUNSELING INFORMATION
   * Sections or subsections omitted from the Full Prescribing Information are not listed.
FULL PRESCRIBING INFORMATION

WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Bronchospasm
ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services [see Warnings and Precautions (5.1, 5.2)]. Facilities must have a short-acting bronchodilator (e.g. albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE [see Dosage and Administration (2.2, 2.4) and Contraindications (4)].

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. ADASUVE is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

ADASUVE is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

“Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior), leading clinicians to the use of rapidly absorbed antipsychotic medications to achieve immediate control of the agitation [see Clinical Studies (14)].

The efficacy of ADASUVE was established in one study of acute agitation in patients with schizophrenia and one study of acute agitation in patients with bipolar I disorder [see Clinical Studies (14)].

Limitations of Use:
As part of the ADASUVE REMS Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility [see Warnings and Precautions (5.2)].
2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

ADASUVE must be administered only by a healthcare professional. ADASUVE is administered by oral inhalation only. The recommended dose for acute agitation is 10 mg administered by oral inhalation, using a single-use inhaler. Administer only a single dose within a 24-hour period [see Warnings and Precautions (5.1)].

2.2 Required Examination Prior to Dosing

Prior to administering ADASUVE, screen all patients for a history of asthma, COPD, or other pulmonary disease, and examine patients (including chest auscultation) for respiratory signs (e.g. wheezing) [see Warnings and Precautions (5.1)].

2.3 Important Administration Instructions

Read all of these instructions prior to administering ADASUVE.

Step 1. Open the Pouch

When ready to use, tear open the foil pouch and remove the inhaler from the package (see Figure 1).

Figure 1. Tearing the pouch

When the ADASUVE inhaler is removed from the pouch, the indicator light is off (see Figure 2).
Figure 2. ADASUVE Inhaler with Indicator Light

Step 2. Pull Tab

Firmly pull the plastic tab from the rear of the inhaler (see Figure 3). Check that the green light turns on. This indicates that the inhaler is ready for use. Use the inhaler within 15 minutes after removing the tab to prevent automatic deactivation of the inhaler. The green light will turn off, indicating that the inhaler is not usable. Discard the inhaler after one use.

Figure 3.

Step 3. Explain Procedures to the Patient

Explain the administration procedures to the patient prior to use, and advise the patient that it is important to follow the instructions. Inform the patient that the inhaler may produce a flash of light and a clicking sound, and it may become warm during use. These are normal.
Step 4. **Instruct the Patient to Exhale**

Instruct the patient to hold the inhaler away from the mouth and breathe out fully to empty the lungs (see Figure 4).

**Figure 4. Exhale**

Step 5. **Instruct the Patient to Inhale**

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 (see Figure 5). Check that the green light turns off indicating that the dose has been delivered.

**Figure 5. Inhale**

Step 6. **Instruct the Patient to Hold Breath**

Instruct the patient to remove the mouthpiece from the mouth and hold the breath for as long as possible, up to 10 seconds (see Figure 6).

**Figure 6. Hold Breath**

Important: If the green light remains on after the patient inhales, the dose of ADASUVE 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.
2.4 Monitoring to Assess Safety
Monitor the patient for signs and symptoms of bronchospasm after ADASUVE administration. Perform a physical examination, including chest auscultation, at least every 15 minutes for at least one hour after ADASUVE administration [see Warnings and Precautions (5.1)].

3 DOSAGE FORMS AND STRENGTHS
ADASUVE is an inhalation powder supplied in a single-use, disposable inhaler containing 10 mg of loxapine base.

4 CONTRAINDICATIONS
ADASUVE is contraindicated in patients with the following:

- Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm [see Warnings and Precautions (5.1)]
- Acute respiratory symptoms or signs (e.g., wheezing) [see Warnings and Precautions (5.1)]
- Current use of medications to treat airways disease, such as asthma or COPD [see Warnings and Precautions (5.1)]
- History of bronchospasm following ADASUVE treatment [see Warnings and Precautions (5.1)]
- Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine.

5 WARNINGS AND PRECAUTIONS
5.1 Bronchospasm
ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest [see Adverse Reactions (6.1)]. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. Facilities must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm [see Boxed Warning and Warnings and Precautions (5.2)].

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history of asthma, COPD, and other lung disease associated with bronchospasm, acute respiratory symptoms or signs, current use of medications to treat airways disease, such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing) [See Dosage and Administration (2.2) and Contraindications (4)]. Monitor patients for symptoms and signs of bronchospasm (i.e., vital signs and chest auscultation) at least every 15 minutes for a minimum of one hour following treatment with ADASUVE [see Dosage and Administration (2.4)]. ADASUVE can cause sedation, which can mask the symptoms of bronchospasm.
Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm, as indicated by changes in forced expiratory volume in 1 second (FEV1), was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose within a 24 hour period.

Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE.

5.2 ADASUVE REMS to Mitigate Bronchospasm

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a REMS called the ADASUVE REMS. [see Boxed Warning and Warnings and Precautions (5.1)] Required components of the ADASUVE REMS are:

- Healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements. Certified healthcare facilities must be able to provide immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services. Facilities must have a short-acting bronchodilator (e.g. albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm.

- Wholesalers and distributors that distribute ADASUVE must distribute only to enrolled healthcare facilities.

Further information is available at www.adasuverems.com or 1-855-755-0492.

5.3 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the cases of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies can be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ADASUVE is not approved for the treatment of elderly patients with dementia-related psychosis [see Boxed Warning].

5.4 Neuroleptic Malignant Syndrome

Antipsychotic drugs can cause a potentially fatal symptom complex termed Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Associated features can include elevated
serum creatine phosphokinase (CPK) concentration, rhabdomyolysis, elevated serum and urine myoglobin concentration, and renal failure. NMS did not occur in the ADASUVE clinical program.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to consider the presence of other serious medical conditions (e.g., pneumonia, systemic infection, heat stroke, primary CNS pathology, central anticholinergic toxicity, extrapyramidal symptoms, or drug fever).

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs that may contribute to the underlying disorder, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Hypotension and Syncope

ADASUVE can cause hypotension, orthostatic hypotension, and syncope. Use ADASUVE with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, or treatment with antihypertensive medications or other drugs that affect blood pressure or reduce heart rate).

In the presence of severe hypotension requiring vasopressor therapy, the preferred drugs may be norepinephrine or phenylephrine. Epinephrine should not be used, because beta stimulation may worsen hypotension in the setting of ADASUVE-induced partial alpha blockade.

In short-term (24-hour) placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar I disorder, hypotension occurred in 0.4% and 0.8% in the ADASUVE 10 mg and placebo groups, respectively. There were no cases of orthostatic hypotension, postural symptoms, presyncope or syncope. A systolic blood pressure ≤ 90 mm Hg with a decrease of ≥ 20 mm Hg occurred in 1.5% and 0.8% of the ADASUVE 10 mg and placebo groups, respectively. A diastolic blood pressure ≤ 50 mm Hg with a decrease of ≥15 mm Hg occurred in 0.8% and 0.4% of the ADASUVE 10 mg and placebo groups, respectively.

In 5 Phase 1 studies in normal volunteers, the incidence of hypotension was 3% and 0% in ADASUVE 10 mg and the placebo groups, respectively. The incidence of syncope or presyncope in normal volunteers was 2.3% and 0% in the ADASUVE and placebo groups, respectively. In normal volunteers, a systolic blood pressure ≤ 90 mm Hg with a decrease of ≥ 20 mm Hg occurred in 5.3% and 1.1% in the ADASUVE and placebo groups, respectively. A diastolic blood pressure ≤ 50 mm Hg with a decrease of ≥ 15 mm Hg occurred in 7.5% and 3.3% in the ADASUVE and placebo groups, respectively.
5.6 Falls

ADASUVE may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.7 Seizures

ADASUVE lowers the seizure threshold. Seizures have occurred in patients treated with oral loxapine. Seizures can occur in epileptic patients even during antiepileptic drug maintenance therapy. In short term (24 hour), placebo-controlled trials of ADASUVE, there were no reports of seizures.

5.8 Potential for Cognitive and Motor Impairment

ADASUVE can impair judgment, thinking, and motor skills. In short-term, placebo-controlled trials, sedation and/or somnolence were reported in 12% and 10% in the ADASUVE and placebo groups, respectively. No patients discontinued treatment because of sedation or somnolence.

The potential for cognitive and motor impairment is increased when ADASUVE is administered concurrently with other CNS depressants [see Drug Interactions (7.1)]. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ADASUVE does not affect them adversely.

5.9 Cerebrovascular Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with atypical antipsychotics in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse reactions (stroke and transient ischemic attacks), including fatalities, compared to placebo-treated patients. ADASUVE is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions (5.3)].

5.10 Anticholinergic Reactions Including Exacerbation of Glaucoma and Urinary Retention

ADASUVE has anticholinergic activity, and it has the potential to cause anticholinergic adverse reactions including exacerbation of glaucoma or urinary retention. The concomitant use of other anticholinergic drugs (e.g., antiparkinson drugs) with ADASUVE could have additive effects.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hypersensitivity (serious skin reactions) [see Contraindications (4)]
• Bronchospasm [see Warnings and Precautions (5.1)]

• Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.3)]

• Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.4)]

• Hypotension and syncope [see Warnings and Precautions (5.5)]

• Seizure [see Warnings and Precautions (5.7)]

• Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.8)]

• Cerebrovascular Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.9)]

• Anticholinergic Reactions Including Exacerbation of Glaucoma and Urinary Retention [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

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

The following findings are based on pooled data from three short-term (24-hour), randomized, double-blind, placebo-controlled clinical trials (Studies 1, 2, and 3) of ADASUVE 10 mg in the treatment of patients with acute agitation associated with schizophrenia or bipolar I disorder. In the 3 trials, 259 patients received ADASUVE 10 mg, and 263 received placebo [see Clinical Studies (14)].

Commonly Observed Adverse Reactions: In the 3 trials in acute agitation, the most common adverse reactions were dysgeusia, sedation, and throat irritation. These reactions occurred at a rate of at least 2% of the ADASUVE group and at a rate greater than in the placebo group. (Refer to Table 1).

Table 1. Adverse Reactions in 3 Pooled Short-Term, Placebo-Controlled Trials (Studies 1, 2, and 3) in Patients with Schizophrenia or Bipolar Disorder

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n = 263)</th>
<th>ADASUVE (n = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>Sedation</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Throat Irritation</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Airway Adverse Reactions in the 3 Trials in Acute Agitation

Agitated patients with Schizophrenia or Bipolar Disorder: In the 3 short-term (24-hour), placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar disorder (Studies 1, 2, and 3), bronchospasm (which includes reports of wheezing, shortness of breath and cough) occurred more frequently in the ADASUVE group, compared to the placebo group: 0% (0/263) in the placebo group and 0.8% (2/259) in the ADASUVE 10 mg group. One patient with schizophrenia, without a history of pulmonary disease, had significant bronchospasm requiring rescue treatment with a bronchodilator and oxygen.

Bronchospasm and Airway Adverse Reactions in Pulmonary Safety Trials

Clinical pulmonary safety trials demonstrated that ADASUVE can cause bronchospasm as measured by FEV1, and as indicated by respiratory signs and symptoms in the trials. In addition, the trials demonstrated that patients with asthma or other pulmonary diseases, such as COPD are at increased risk of bronchospasm. The effect of ADASUVE on pulmonary function was evaluated in 3 randomized, double-blind, placebo-controlled clinical pulmonary safety trials in healthy volunteers, patients with asthma, and patients with COPD. Pulmonary function was assessed by serial FEV1 tests, and respiratory signs and symptoms were assessed. In the asthma and COPD trials, patients with respiratory symptoms or FEV1 decrease of $\geq 20\%$ were administered rescue treatment with albuterol (metered dose inhaler or nebulizer) as required. These patients were not eligible for a second dose; however, they had continued FEV1 monitoring in the trial.

Healthy Volunteers: In the healthy volunteer crossover trial, 30 subjects received 2 doses of either ADASUVE or placebo 8 hours apart, and 2 doses of the alternate treatment at least 4 days later. The results for maximum decrease in FEV1 are presented in Table 2. No subjects in this trial developed airway related adverse reactions (cough, wheezing, chest tightness, or dyspnea).

Asthma Patients: In the asthma trial, 52 patients with mild-moderate persistent asthma (with FEV1 $\geq 60\%$ of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose. Approximately 67% of these patients had a baseline FEV1 $\geq 80\%$ of predicted. The remaining patients had an FEV1 60-80% of predicted. Nine patients (17%) were former smokers. As shown in Table 2 and Figure 7, there was a marked decrease in FEV1 immediately following the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 303 mL and 9.1%, respectively). Furthermore, the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 537 mL and 14.7 %, respectively). Respiratory-related adverse reactions (bronchospasm, chest discomfort, cough, dyspnea, throat tightness, and wheezing) occurred in 54% of ADASUVE-treated patients and 12% of placebo-treated patients. There were no serious adverse events. Nine of 26 (35%) patients in the ADASUVE group, compared to one of 26 (4%) in the placebo group, did not receive a second dose of study medication, because they had a $\geq 20\%$ decrease in FEV1 or they developed respiratory symptoms after the first dose. Rescue medication (albuterol via metered dose inhaler or nebulizer) was administered to 54% of patients in the ADASUVE group [7 patients (27%) after the first dose and 7 of the
remaining 17 patients (41%) after the second dose] and 12% in the placebo group (1 patient after the first dose and 2 patients after the second dose).

COPD Patients: In the COPD trial, 53 patients with mild to severe COPD (with FEV1 ≥ 40% of predicted) were randomized to treatment with 2 doses of ADASUVE 10 mg or placebo. The second dose was to be administered 10 hours after the first dose. Approximately 57% of these patients had moderate COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II]; 32% had severe disease (GOLD Stage III); and 11% had mild disease (GOLD Stage I). As illustrated in Table 2 there was a decrease in FEV1 soon after the first dose (maximum mean decreases in FEV1 and % predicted FEV1 were 96 mL and 3.5%, respectively), and the effect on FEV1 was greater following the second dose (maximum mean decreases in FEV1 and % predicted FEV1 were 125 mL and 4.5%, respectively). Respiratory adverse reactions occurred more frequently in the ADASUVE group (19%) than in the placebo group (11%). There were no serious adverse events. Seven of 25 (28%) patients in the ADASUVE group and 1 of 27 (4%) in the placebo group did not receive a second dose of study medication because of a ≥ 20% decrease in FEV1 or the development of respiratory symptoms after the first dose. Rescue medication (albuterol via MDI or nebulizer) was administered to 23% of patients in the ADASUVE group: 8% of patients after the first dose and 21% of patients after the second dose, and to 15% of patients in the placebo group.

**Table 2: Maxium Decrease in FEV1 from Baseline in the Healthy Volunteer, Asthma, and COPD Trials**

<table>
<thead>
<tr>
<th>Maximum % FEV1 ↓</th>
<th>Healthy Volunteer</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n (%)</td>
<td>ADASUVE 10 mg n (%)</td>
<td>Placebo n (%)</td>
</tr>
<tr>
<td>After any Dose</td>
<td>N=26</td>
<td>N=26</td>
<td>N=26</td>
</tr>
<tr>
<td>≥10</td>
<td>7 (27)</td>
<td>7 (27)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>≥15</td>
<td>1 (4)</td>
<td>5 (19)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>After Dose 1</td>
<td>N=26</td>
<td>N=26</td>
<td>N=26</td>
</tr>
<tr>
<td>≥10</td>
<td>4 (15)</td>
<td>5 (19)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>≥15</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>After Dose 2</td>
<td>N=26</td>
<td>N=25</td>
<td>N=25</td>
</tr>
<tr>
<td>≥10</td>
<td>5 (19)</td>
<td>6 (24)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>≥15</td>
<td>0</td>
<td>5 (20)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>≥20</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

FEV1 categories are cumulative; i.e. a subject with a maximum decrease of 21% is included in all 3 categories. Patients with a ≥ 20% decrease in FEV1 did not receive a second dose of study drug.
Patients with a $\geq 20\%$ decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10.

**Extrapyramidal Symptoms (EPS):** Extrapyramidal reactions have occurred during the administration of oral loxapine. In most patients, these reactions involved parkinsonian symptoms such as tremor, rigidity, and masked facies. Akathisia (motor restlessness) has also occurred.

In the 3 short-term (24-hour), placebo-controlled trials of ADASUVE in 259 patients with agitation associated with schizophrenia or bipolar disorder, extrapyramidal reactions occurred. One patient (0.4%) treated with ADASUVE developed neck dystonia and oculogyration. The incidence of akathisia was 0% and 0.4% in the placebo and ADASUVE groups, respectively.

**Dystonia (Antipsychotic Class Effect):** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during treatment with ADASUVE. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, difficulty swallowing or breathing, and/or protrusion of the tongue.

Acute dystonia tends to be dose-related, but can occur at low doses, and occurs more frequently with first generation antipsychotic drugs such as ADASUVE. The risk is greater in males and younger age groups.

**Cardiovascular Reactions:** Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope have been reported with oral administration of loxapine.
7 DRUG INTERACTIONS

7.1 CNS Depressants

ADASUVE is a central nervous system (CNS) depressant. The concurrent use of ADASUVE with other CNS depressants (e.g., alcohol, opioid analgesics, benzodiazepines, tricyclic antidepressants, general anesthetics, phenothiazines, sedative/hypnotics, muscle relaxants, and/or illicit CNS depressants) can increase the risk of respiratory depression, hypotension, profound sedation, and syncope. Therefore, consider reducing the dose of CNS depressants if used concomitantly with ADASUVE.

7.2 Anticholinergic Drugs

ADASUVE has anticholinergic activity. The concomitant use of ADASUVE and other anticholinergic drugs can increase the risk of anticholinergic adverse reactions including exacerbation of glaucoma and urinary retention.

8 USE IN SPECIFIC POPULATIONS

In general, no dose adjustment for ADASUVE is required on the basis of a patient’s age, gender, race, smoking status, hepatic function, or renal function.

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of ADASUVE use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. 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. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

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

Animal Data

In rats, embryofetal toxicity (increased fetal resorptions, reduced weights, and hydronephrosis with hydroureter) was observed following oral administration of loxapine during the period of organogenesis at a dose of 1 mg/kg/day. This dose is equivalent to the
MRHD of 10 mg/day on a mg/m$^2$ basis. In addition, fetal toxicity (increased prenatal death, decreased postnatal survival, reduced fetal weights, delayed ossification, and/or distended renal pelvis with reduced or absent papillae) was observed following oral administration of loxapine from mid-pregnancy through weaning at doses of 0.6 mg/kg and higher. This dose is approximately half the MRHD of 10 mg/day on a mg/m$^2$ basis.

No teratogenicity was observed following oral administration of loxapine during the period of organogenesis in the rat, rabbit, or dog at doses up to 12, 60, and 10 mg/kg, respectively. These doses are approximately 12-, 120-, and 32-fold the MRHD of 10 mg/day on a mg/m$^2$ basis, respectively.

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety and effectiveness of ADASUVE in pediatric patients have not been established.

### 8.5 Geriatric Use

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death [see Boxed Warning and Warnings and Precautions (5.3)]. ADASUVE is not approved for the treatment of dementia-related psychosis. Placebo-controlled studies of ADASUVE in patients with agitation associated with schizophrenia or bipolar disorder did not include patients over 65 years of age.

### 10 OVERDOSAGE

#### Signs and Symptoms of Overdose

As would be expected from the pharmacologic actions of loxapine, the clinical findings may include CNS depression, unconsciousness, profound hypotension, respiratory depression, extrapyramidal symptoms, and seizure.

#### Management of Overdose

For the most up to date information on the management of ADASUVE overdose, contact a certified poison control center (1-800-222-1222 or www.poison.org). Provide supportive care including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.
11 DESCRIPTION

ADASUVE, a typical antipsychotic, is an inhalation powder of loxapine supplied in a single-use, disposable inhaler containing 10 mg of loxapine base. ADASUVE is a drug-device combination product.

Active Ingredient: Loxapine (base). Loxapine, a dibenzoxazepine compound, represents a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Chemically, it is 2-Chloro-11-(4-methyl-1-piperazinyl) dibenz[b,f][1,4] oxazepine.

\[ C_{18}H_{18}ClN_3O \]

ADASUVE is a single-use, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally-generated drug vapor. The vapor condenses into aerosol particles that are dispersed into the airstream created by the patient inhaling through the mouthpiece.

Each product is packaged inside a sealed foil pouch. The product is a white to off-white plastic unit, with a mouthpiece on one end and a pull-tab protruding from the other end.

Removal of a pull-tab from the product renders it ready for use, as indicated by illumination of a green light. After inhalation through the mouthpiece, successful dosing is signaled by the green light turning off.

Under standardized in vitro test conditions, ADASUVE, 10 mg delivers 9.1 mg of loxapine out of the mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of loxapine in the treatment of agitation associated with schizophrenia is unknown. However, its efficacy could be mediated through a combination of antagonism of central dopamine D₂ and serotonin 5-HT₂A receptors. The mechanism of action of loxapine in the treatment of agitation associated with bipolar I disorder is unknown.

12.2 Pharmacodynamics

Loxapine acts as an antagonist at central serotonin and dopamine receptors, with high affinity for serotonin 5-HT₂A and dopamine D₁, D₂, D₃, and D₄ receptors (Kᵢ values of 2 nM, 18 nM, 10 nM, 21 nM, 9 nM, respectively). Some of the adverse effects of loxapine may be related to the antagonism of histamine H₁ (somnolence), muscarinic M1 (anticholinergic), and
adrenergic α2 (orthostatic hypotension) receptors (Kᵢ values of 15 nM, 117 nM and 250 nM, respectively).

**Thorough QTc Study**

ADASUVE did not prolong the QTc interval. The effect of ADASUVE on QTc prolongation was evaluated in a randomized, double-blinded, positive- (moxifloxacin 400 mg) and placebo-controlled parallel study in healthy subjects. A total of 48 healthy subjects were administered ADASUVE 10 mg. In this study with a demonstrated ability to detect small effects, the upper bound of the 90% confidence interval (CI) for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method was below 10 milliseconds, the threshold for regulatory concern.

**12.3 Pharmacokinetics**

*Absorption:* The single-dose pharmacokinetic parameters of loxapine following administration of single doses of ADASUVE 10 mg in healthy adult subjects are presented in Table 3 and Figure 8.

Administration of ADASUVE resulted in rapid absorption of loxapine, with a median time of maximum plasma concentration (Tₘₐₓ) of 2 minutes. Loxapine exposure in the first 2 hours after administration (AUC₀–₂ₙ₉) was 66.7 ng•h/mL for the 10 mg dose. As a consequence of the very rapid absorption of loxapine after oral inhalation, there is substantial variability in the early plasma concentrations of loxapine. The mean plasma loxapine concentrations following administration of ADASUVE were linear over the clinical dose range. AUC₀–₂ₙ₉, AUCₘᵢₓ, and Cₘᵢₓ increased in a dose-dependent manner.

**Table 3. Pharmacokinetics in Healthy Adult Subjects Administered a Single Dose of ADASUVE 10 mg**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADASUVE 10 mg (N=114)</td>
</tr>
<tr>
<td>AUC₀–₂ₙ₉ (ng•h/mL), mean ± SD</td>
<td>66.7 ± 18.2</td>
</tr>
<tr>
<td>AUCₘᵢₓ (ng•h/mL), mean ± SD</td>
<td>188 ± 47</td>
</tr>
<tr>
<td>Cₘᵢₓ (ng/mL), mean ± SD</td>
<td>257 ± 219</td>
</tr>
<tr>
<td>Tₘᵢₓ (minutes), median (25%, 75%)</td>
<td>1.13 (1, 2)</td>
</tr>
<tr>
<td>Half-life(h), mean ± SD</td>
<td>7.61 ± 1.87</td>
</tr>
</tbody>
</table>
**Figure 8.** Mean Plasma Concentrations of Loxapine following Single-Dose Administration ADASUVE 10 mg in Healthy Subjects

\[ \text{Graph showing mean plasma concentrations of Loxapine over time.} \]

**Distribution:** Loxapine is removed rapidly from the plasma and distributed in tissues. Animal studies following oral administration suggest an initial preferential distribution in the lungs, brain, spleen, heart, and kidney. Loxapine is 96.6% bound to human plasma proteins.

**Metabolism:** Loxapine is metabolized extensively in the liver following oral administration, with multiple metabolites formed. The main metabolic pathways include: 1) hydroxylation to form 8-OH-loxapine by CYP1A2 and 7-OH-loxapine by CYP3A4 and CYP2D6, 2) N-oxidation to form loxapine N-oxide by flavanoid monoamine oxidases (FMOs), and 3) de-methylation to form amoxapine. Because there are multiple metabolic pathways, the risk of metabolic interactions caused by an effect on an individual isoform is minimal. For ADASUVE, the order of metabolites observed in humans (based on systemic exposure) was 8-OH-loxapine >> loxapine N-oxide, 7-OH-loxapine > amoxapine. Plasma levels of 8-OH-loxapine are similar to those of the parent compound.

**Excretion:** Excretion occurs mainly in the first 24 hours. Metabolites are excreted in the urine in the form of conjugates and in the feces unconjugated. The terminal elimination half-life ($T_{1/2}$) ranged from 6 to 8 hours.

**Transporter Interaction:** *In vitro* studies indicated that loxapine was not a substrate for p-glycoprotein (P-gp); however, loxapine inhibited P-gp.
Special Populations:

Pharmacokinetics in Smokers: Loxapine exposures in nonsmokers and smokers are similar, with geometric mean ratios of 92%, 85%, and 99% for AUC\textsubscript{0-2h}, AUC\textsubscript{inf}, and C\textsubscript{max} respectively. No dosage adjustment is recommended based on smoking status.

Demographic Effects: There were no clinically significant differences in loxapine pharmacokinetics following administration of ADASUVE in subgroups based on age, weight, body mass index, gender, or race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No adequate studies have been conducted.

Mutagenesis: Loxapine did not cause mutation or chromosomal aberration when tested \textit{in vitro} and \textit{in vivo}. Loxapine was negative in the Ames gene mutation assay, the human peripheral blood lymphocyte chromosomal aberration assay, and in the \textit{in vivo} mouse bone marrow micronucleus assay up to 40 mg/kg (20-fold the MRHD on mg/m\textsuperscript{2} basis).

Loxapine metabolite 8-OH-loxapine was not mutagenic in the \textit{in vitro} Ames reverse mutation assay and was not clastogenic in the \textit{in vitro} human peripheral blood lymphocyte chromosomal aberration assay.

Impairment of Fertility: Loxapine had no effects on fertility or early embryonic development in male rats or in male and female rabbits following oral administration. Mating was decreased in female rats because these animals were in persistent diestrus, an expected pharmacologic effect for this class of compounds. This occurred at doses approximately 0.2- and 1-fold the MRHD of 10 mg/day on a mg/m\textsuperscript{2} basis.

13.2 Animal Toxicology and/or Pharmacology

In the rat, minimal and reversible squamous metaplasia of the larynx was observed after daily inhalation exposure of loxapine for 14 days at 1.7 to 13 mg/kg/day (approximately 2- to 13-fold the MRHD of 10 mg/day on a mg/m\textsuperscript{2} basis, respectively). This finding was considered a nonspecific particle impaction effect. Mammary hyperplasia in males and females and ovarian follicular cysts and mucification of vaginal epithelium in female rats were observed at all doses, with partial or complete recovery at the end of 14 days of treatment. In the dog, no effects on the respiratory tract or reproductive tissues were observed after inhalation exposure to loxapine for 28 days at doses up to 1.8 mg/kg/day (approximately 6-fold the MRHD of 10 mg/day on a mg/m\textsuperscript{2} basis).

14 CLINICAL STUDIES

The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with schizophrenia or bipolar I disorder was established in two short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trials. Study 1 included 344 patients who met
DSM-IV criteria for schizophrenia. Study 2 included 314 patients who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features.

Patients were judged by the clinical investigators to be clinically agitated, with a level of agitation that met or exceeded a specific severity threshold as measured by the Positive and Negative Syndrome Scale-Excited Component (PEC). The PEC is an investigator-rated instrument consisting of 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). Thus, the total PEC score can range from 5 to 35. For enrollment in the studies, patients had to have a PEC score of ≥ 14, with at least one individual item score ≥ 4.

Patients whose agitation was related to acute alcohol or drug intoxication were excluded. Patients with clinically significant acute or chronic pulmonary disease (e.g., asthma, COPD, chronic bronchitis, and emphysema) were excluded from the trials [See Contraindications (4)].

The primary efficacy endpoint in both trials was the mean change from baseline in the PEC score, assessed 2 hours following dosing. The key secondary endpoint was the mean Clinical Global Impression Improvement (CGI-I) Scale score at two hours. The CGI-I is an investigator-rated global assessment of symptom improvement, scored on a scale of 1 to 7: 1 = very much improved; 4 = no change from baseline; 7 = very much worse.

In both studies, mean baseline PEC scores were similar in all treatment groups, averaging 17.3 to 17.7 (Table 4), with individual patient scores ranging from 14 to 31, indicating predominantly moderate levels of agitation. The mean baseline Clinical Global Impression Severity Scale (CGI-S) score in both studies was 4 (moderately ill). In Study 2, 69% of patients had a current manic episode, and 31% had a mixed/manic episode.

In Studies 1 and 2, treatment with ADASUVE was statistically significantly superior to placebo on the mean change in PEC score at 2 hours (Table 4). In both studies, the effect of ADASUVE was apparent at 10 minutes following dosing (Figures 9 and 10).
### Table 4. Change from Baseline in the PEC Score at 2 Hours Post-Dose in the Schizophrenia (Study 1) and Bipolar I Disorder (Study 2) Trials

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ADASUVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1 (Schizophrenia)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>112</td>
</tr>
<tr>
<td>PEC score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>17.4</td>
<td>17.6</td>
</tr>
<tr>
<td>Change at 2 hours(^a)</td>
<td>-5.8</td>
<td>-8.7</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)(^b)</td>
<td>--</td>
<td>-2.9 (-4.2, -1.6)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

| **Study 2 (Bipolar Disorder)** |         |         |
| N                    | 105     | 105     |
| PEC score            |         |         |
| Mean baseline        | 17.7    | 17.3    |
| Change at 2 hours\(^a\) | -4.7    | -9.2    |
| Difference from placebo (95% CI)\(^b\) | --      | -4.5 (-5.8, -3.1) |
| p-value              | --      | < 0.0001 |

\(^a\) Least squares mean for the difference defined as the change from baseline

\(^b\) Least squares mean for the difference defined as the change from baseline at hour 2 in the drug group minus that in the placebo group.

Examination of population subsets (age, race, and gender) on the primary endpoint did not reveal any differential responsiveness on the basis of these subgroupings.

Figures 9 and 10 show the decreases in PEC score at each time point assessed in the trials. In both trials, the decrease in agitation with ADASUVE was apparent at each time point tested (10, 20, 30, 45, 60, 90, and 120 minutes post-dose).
Figure 9.  Mean Change from Baseline in PEC Score through 2 Hours after a Single Dose in Agitated Patients with Schizophrenia (Study 1)

Figure 10.  Mean Change from Baseline in PEC Score through 2 Hours after a Single Dose in Agitated Patients with Bipolar Disorder (Study 2)

The results of the secondary endpoint, CGI-I scores, are shown in Table 5.
<table>
<thead>
<tr>
<th>Study 1 (Schizophrenia)</th>
<th>Placebo</th>
<th>ADASUVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>115</td>
<td>112</td>
</tr>
<tr>
<td>CGI-I score at 2 hours&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>-</td>
<td>-0.8 (-1.1, -0.4)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2 (Bipolar Disorder)</th>
<th>Placebo</th>
<th>ADASUVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>CGI-I score at 2 hours&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>-1.1 (-1.4, -0.8)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Least squares mean

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

ADASUVE® (loxapine) inhalation powder is supplied as:

ADASUVE 10 mg (NDC 10885-003-01) is a single-use, disposable inhaler containing 10 mg of loxapine, provided in a sealed foil pouch. ADASUVE, 10 mg is supplied in a carton of 5 units per carton (NDC 10885-003-05).

#### 16.2 Restricted Access

ADASUVE is only available through a restricted program called the ADASUVE REMS Program [see Warnings and Precautions (5.2)].

#### 16.3 Storage and Handling

Store ADASUVE at room temperature, 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

Keep ADASUVE in pouch until time of use.

ADASUVE contains a lithium battery. Dispose of ADASUVE in accordance with all federal, state and local laws.
17  PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

**Bronchospasm**

Advise patients and caregivers that there is a risk of bronchospasm. Advise patients to inform their healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE [see Boxed Warning and Warnings and Precautions (5.1)]

**Interference with Cognitive and Motor Performance**

Caution patients and caregivers about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that ADASUVE has not affected them adversely [see Warnings and Precautions (5.8)].

Caution patients and caregivers about the potential for sedation, especially when used concurrently with other CNS depressants (e.g., alcohol, opioid analgesics, benzodiazepines, tricyclic antidepressants, general anesthetics, phenothiazines, sedative/hypnotics, muscle relaxants, and/or illicit CNS depressants).

**Neuroleptic Malignant Syndrome**

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [see Warnings and Precautions (5.4)].

**Hypotension and Syncope**

Advise patients and caregivers of the risk of hypotension or orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) [see Warnings and Precautions (5.5)].

**Anticholinergic Reactions**

Counsel patients and caregivers about the potential risks of anticholinergic reactions, such as exacerbation of glaucoma and urinary retention [see Warnings and Precautions (5.10)].

**Pregnancy**

Counsel patients and caregivers regarding the potential risk to the fetus or neonate [see Use in Specific Populations (8.1)].
Nursing Mothers

Counsel patients and caregivers regarding the potential risk to the infant [see Use in Specific Populations (8.3)].

Manufactured for: Galen US Inc., 25 Fretz Road, Souderton, PA 18964

MEDICATION GUIDE

ADASUVE® (AD-uh-soov)

(loxapine)

Inhalation Powder

Read this Medication Guide before you start taking ADASUVE and each time it is given to you. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about ADASUVE?

ADASUVE is available only through the ADASUVE Risk Evaluation and Mitigation Strategy (REMS) Program. The healthcare facility must be enrolled in the ADASUVE REMS Program before you can be given ADASUVE.

ADASUVE may cause serious side effects, including:

• Narrowing of the airways (bronchospasm) that can cause you to have problems breathing or to stop breathing. People who have asthma or other airway or lung problems, such as chronic obstructive pulmonary disease (COPD), have a higher risk of bronchospasm when taking ADASUVE. Symptoms of bronchospasm may include:
  o wheezing
  o coughing
  o chest tightness
  o shortness of breath
  Tell your healthcare provider right away if you have any of these symptoms of bronchospasm after taking ADASUVE.
  Your healthcare provider should check you for breathing problems before and after you take ADASUVE.

• Increased risk of death in elderly patients with dementia-related psychosis. Medicines like ADASUVE can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ADASUVE is not approved for the treatment of patients with dementia-related psychosis.
What is ADASUVE?
ADASUVE is a prescription medicine that is inhaled through your mouth and is used to treat acute agitation in adults with schizophrenia or bipolar I disorder. It is not known if ADASUVE is safe and effective in children.

Who should not take ADASUVE?
Do not take ADASUVE if you:

- have or have had asthma, chronic obstructive pulmonary disease (COPD), or other airway or lung problems that can cause bronchospasm
- are having problems with wheezing, coughing, chest tightness, or shortness of breath
- are taking medicines to treat asthma or COPD
- have taken ADASUVE before and had bronchospasm
- are allergic to loxapine or amoxapine

What should I tell my healthcare provider before taking ADASUVE?
Before you take ADASUVE, tell your healthcare provider if you:

- have high or low blood pressure
- have or have had heart problems or stroke
- have or have had seizures (convulsions)
- drink alcohol or use street drugs
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if ADASUVE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ADASUVE passes into your breast milk. You and your healthcare provider should decide if you will take ADASUVE if you are breastfeeding.

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

- ADASUVE and other medicines may affect each other causing side effects. ADASUVE may affect the way other medicines work, and other medicines may affect the way ADASUVE works.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.
How should I take ADASUVE?

- Your healthcare provider will show you how to take ADASUVE right before you take it.
- Take ADASUVE exactly as your healthcare provider shows you to take it.
- ADASUVE is for oral inhalation only.

What should I avoid while taking ADASUVE?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ADASUVE affects you.
- Do not drink alcohol while taking ADASUVE. It can increase your chances of getting serious side effects.

What are the possible side effects of ADASUVE?

ADASUVE can cause serious side effects, including:

- See “What is the most important information I should know about ADASUVE?”
- neuroleptic malignant syndrome (NMS). NMS is a rare but serious condition that may cause death. Symptoms of NMS may include:
  - high fever
  - stiff muscles
  - confusion
  - sweating
  - changes in pulse, heart rate, and blood pressure
  Tell your healthcare provider right away if you have any of these symptoms of NMS after taking ADASUVE.
- low blood pressure (hypotension), lightheadedness, or fainting
- seizures (convulsions)
- severe sleepiness and difficulty with potentially dangerous activities such as driving
- worsening of glaucoma
- difficulty urinating

The most common side effects of ADASUVE include:

- bad, bitter, or metallic taste in your mouth (dysgeusia)
- sleepiness (especially when used with other drugs that cause sleepiness)
- sore throat

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of ADASUVE. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of ADASUVE.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about ADASUVE. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ADASUVE that is written for health professionals.

For more information, go to www.ADASUVE.com or call 1-800-284-0062.

**What are the ingredients in ADASUVE?**

**Active Ingredient:** loxapine

**Inactive Ingredients:** none

This Medication Guide has been approved by the U.S. Food and Drug Administration

Manufactured for: Galen US Inc., 25 Fretz Road, Souderton, PA 18964

Rev. 08/2017