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Disclosure: Dr. Valdes and Mr. Shipley report that they have no financial or commercial relationships in regard to this article. Dr. Rey is a consultant for Janssen Pharmaceutical, Otsuka America Pharmaceutical, Inc., and Sunovion Pharmaceuticals, and a common stockholder of Alexza Pharmaceuticals and Alkermes PLC.

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INTRODUCTION
Schizophrenia is a disabling chronic mental illness that is ranked by the World Health Organization among the top 10 illnesses that contribute to the global burden of disease. Approximately 1% of people living in the United States have this illness. Lifetime prevalence of schizophrenia can range from 0.3% to 0.7% without variation based on race, ethnicity, culture, or geographic location. Social and occupational functioning are significantly reduced with the disease, which makes attaining and maintaining employment difficult and can interfere with continuing education, since psychotic features usually emerge between the late teens and mid-30s. Clinical manifestations of schizophrenia can present in a range of ways, such as positive and/or negative symptoms, cognitive impairment, dysphoric mood, anxiety, abnormalities in sensory processing, and lack of insight. Lack of insight increases the risk of non-adherence, relapse, and aggression.

Aggressive behavior in general may be more common in bipolar disorder than in other psychiatric disorders. Studies have found physical aggression was higher in patients with bipolar disorder (75%) compared with other psychiatric disorders. Lifetime prevalence of bipolar I disorder is similar to that of schizophrenia at 1%, with a mean age at onset of approximately 18 years. Mania, the classic symptom of bipolar I, is classified as having an abnormally, persistently elevated, expansive, and/or irritable mood with increased levels of energy/activity for most of the day, almost every day for a week or longer. Often described as “feeling on top of the world,” patients do not perceive that they are ill or in need of treatment. While some individuals become more sexually provocative or have excessive optimism and feelings of grandiosity, others may become hostile and physically threatening. These actions can quickly escalate and lead to physical assault and even emergency room visits.

This state of motor restlessness and mental tension puts emergency room patients and staff at an increased risk for injury. Agitation may necessitate the use of physical restraints, seclusion, or psychotropics to calm the patient. Antipsychotic medications are the treatments of choice, as they have been shown in several clinical trials to address the symptoms and behaviors associated with schizophrenia and agitation. Sedating benzodiazepines are often prescribed to patients with a history of aggression in an effort to reduce episodes; however, aggression often requires emergency treatment with “as needed” medications, typically in an oral or injectable formulation. Speed of onset is the most important factor in choosing a route of administration, according to the Expert Consensus Guidelines for Treatment of Behavioral Emergencies. While oral drugs are generally slower to act than intramuscular injections, some intramuscular formulations have a delayed onset, taking up to 60 minutes to act. Thus the need for a fast-acting, effective, and well-tolerated mechanism is evident.

Loxapine inhalation powder (Adasuve, Teva), approved by the FDA on December 21, 2012, utilizes an antipsychotic with more than three decades of experience in a novel delivery system for the treatment of agitation associated with schizophrenia or bipolar mania.

PHARMACOLOGY AND MECHANISM OF ACTION
Loxapine is regarded as a dibenzoxazepine compound found in a subclass of tricyclic antipsychotic agents, chemically distinct from many antipsychotics available in the thioxanthene, butyrophenone, and phenothiazine classes. Chemically, 2-Chloro-11-(4-methyl-1-piperazinyl) dibenz[b,f][1,4]oxazine has a molecular formula of C_{18}H_{18}ClN_{3}O and a melting point of 109 to 110 degrees Celsius.

Adasuve utilizes a Staccato delivery system developed by Alexza. This single-use device and drug film combination allows rapid systemic delivery of loxapine via inhalation through thermally generated aerosolization of the excipient-free product. Aerosolization is achieved by pulling a tab on the opposed end of the mouthpiece to initiate the heating process. Heating of the film inside the unit is rapid and even to prevent denaturing of the drug; this allows vaporization of the product, which condenses into aerosol particles. Illumination of a green light indicates that the product is ready to be inhaled. The aerosolized product is dispersed into the airstream created by the patient inhaling through the mouthpiece. After inhalation, the green light shuts off, indicating a dose has been delivered successfully. A 10-mg dose of Adasuve delivers 9.1 mg of loxapine, according to in vitro tests. Each unit is packaged inside a sealed foil pouch.

Loxapine exerts its antipsychotic effect by acting as an antagonist at central serotonin and dopamine receptors. Loxapine has high affinity for D_1, D_2, and D_3 receptors.
Table 1 Summary of Clinical Trials of Inhaled Loxapine

<table>
<thead>
<tr>
<th>Study Subject</th>
<th>Allen et al.(^{13})</th>
<th>Lesem et al.(^{14})</th>
<th>Kwentus et al.(^{5})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study subjects</td>
<td>129 patients ages 18–65; DSM-IV criteria for schizophrenia, schizoaffective disorder, schizophreniform, and visible agitation</td>
<td>344 patients ages 18–65; DSM-IV diagnosis of schizophrenia and clinically agitated</td>
<td>314 patients ages 18–65; DSM-IV diagnosis of bipolar I (manic or mixed manic) confirmed with MINI and clinically agitated</td>
</tr>
<tr>
<td>Primary objective</td>
<td>Assess efficacy and safety of inhaled loxapine</td>
<td>Assess efficacy of 1 to 3 doses of inhaled loxapine</td>
<td></td>
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<tr>
<td>Study design</td>
<td>Single-dose, randomized, double-blind, placebo-controlled, parallel-group study comparing 5 mg and 10 mg of inhaled loxapine with inhaled placebo</td>
<td>Repeat-dose, randomized, double-blind, placebo-controlled, parallel-group study comparing 5 mg and 10 mg of inhaled loxapine with inhaled placebo</td>
<td></td>
</tr>
<tr>
<td>Primary efficacy endpoints</td>
<td>Absolute change in PANSS-EC score from baseline to 2 hours following dose 1 of inhaled loxapine</td>
<td>Statically significant for 10 mg vs. placebo ((P = 0.0002))</td>
<td>Statically significant decrease for 10 mg and 5 mg inhaled loxapine vs. placebo ((P &lt; 0.0001) in both studies)</td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td>1. Change in PANSS-EC from baseline at any time over 24 hours 2. Change in CGI-I at 2 hours after dose 1 3. Frequency of CGI-I responses achieving a score of 1 (very much improved) and/or 2 (much improved) at 2 hours after dose 1 4. Change from baseline in BARS score at any time over 24 hours after dose 1</td>
<td>1. Significant for both strengths vs. placebo at 10 minutes ((P &lt; 0.05)) 2. Significant for both strengths at 10 mg ((P = 0.0003) vs. placebo) 3. Significant decrease for both 5 mg ((P = 0.0003)) and 10 mg ((P = 0.0003)) vs. placebo 4. Significant at 2 hours for 10 mg inhaled loxapine ((P &lt; 0.0001))</td>
<td>1. Significant for both strengths vs. placebo at 10 minutes ((P = 0.0001) for 5 mg, (P &lt; 0.0001) for 10 mg) 2. Significant decrease for 5 mg ((P &lt; 0.0001)) and 10 mg ((P &lt; 0.0001)) vs. placebo 3. Significant for 5 mg (66%) and 10 mg (75%) ((P = 0.0001))</td>
</tr>
<tr>
<td>Secondary efficacy endpoint results</td>
<td>1. Significant for 10 mg vs. placebo at 20 minutes ((P &lt; 0.05)) 2. Significant for both 5 mg ((P = 0.0067)) and 10 mg ((P = 0.0003)) vs. placebo 3. Significant decrease for both 5 mg ((P = 0.0007)) and 10 mg ((P = 0.0003)) vs. placebo 4. Significant at 2 hours for 10 mg inhaled loxapine ((P &lt; 0.0001))</td>
<td>1. Significant for both strengths vs. placebo at 10 minutes ((P = 0.0003) for 5 mg, (P &lt; 0.0001) for 10 mg) 2. Significant difference in CGI-I scores at 2 hours for 5 mg (2.3) and 10 mg (2.1) vs. placebo (2.8) ((P = 0.0015) for 5 mg; (P &lt; 0.0001) for 10 mg) 3. Significantly greater for 5 mg (57%) and 10 mg (67%) vs. placebo (36%) ((P = 0.0015) for 5 mg, (P &lt; 0.0001) for 10 mg)</td>
<td>1. Significant for both strengths vs. placebo at 10 minutes ((P = 0.0001) for 5 mg, (P &lt; 0.0001) for 10 mg) 2. Significant decrease for 5 mg ((P &lt; 0.0001)) and 10 mg ((P &lt; 0.0001)) vs. placebo 3. Significant for 5 mg (66%) and 10 mg (75%) ((P = 0.0001))</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Most frequently reported for 5 mg and 10 mg, respectively: dysgeusia (4%, 17%), somnolence (4%, 10%), dizziness (11%, 5%)</td>
<td>For 5 mg and 10 mg, respectively: sedation (12.9%, 10.6%); dysgeusia (8.6%, 10.6%); dizziness (5.2%, 10.6%); hypoaesthesia (0.9%, 3.5%); headache (2.6%, 2.7%); somnolence (2.6%, 2.7%); nausea (0.9%, 1.8%). Serious: wheezing/bronchospasms (n = 3), neck dystonia/oculogyration (n = 1), severe sedation (n = 1); coughing (n = 1)</td>
<td>For 5 mg and 10 mg, respectively: sedation (6.7%, 5.7%); dysgeusia (17.3%, 17.1%); dizziness (5.8%, 4.8%); fatigue (3.8, 2.9%); headache (3.8%, 1.9%); stomach discomfort (2.9%, 1%) throat irritation (0%, 3.8%). Moderate akathisia (n = 1); hypotension (n = 1); hypertension (n = 1); anxiety (n = 2). No coughing, wheezing, or bronchospasm reported*</td>
</tr>
</tbody>
</table>

BARS = Behavioral Activity Rating Scale; CGI-I = Clinical Global Impression–Improvement Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MINI = Mini International Neuropsychiatric Interview; PANSS–EC = Positive and Negative Syndrome Scale–Excited Component

* This finding is likely due to the addition of an exclusion criterion preventing patients with an acute or chronic pulmonary condition from participating.
D₃, and D₄ receptors and 5-HT₂A receptors. Treatment of agitation is not fully understood, but loxapine possesses moderate anticholinergic activity (via muscarinic M1 antagonism), strong α₁- and α₂-adrenergic receptor antagonism, and moderate histaminergic antagonism (via histamine [H₁] receptors). Antagonism of α₁-adrenergic as well H₂ receptors is thought to be responsible for the sedation caused by loxapine administration.¹¹

**PHARMACOKINETICS**

**Absorption**
Administration of Adasuve results in rapid absorption with a Tₘₐₓ of two minutes, reaching a mean maximum plasma concentration (Cₘₐₓ) of 257 ng/mL plus or minus 219 ng/mL. Exposure in the first two hours after administration of a 10-mg dose was 66.7 ng•h/mL.¹¹

**Distribution**
After inhalation, animal studies show an initial preferential distribution in the lungs, brain, spleen, heart, and kidneys. Loxapine is removed rapidly from the body; 96.6% is protein-bound.¹¹

**Metabolism**
Loxapine is hepatically metabolized following oral administration through multiple metabolic pathways. Hydroxyl-ation, N-oxidation, and de-methylation form 8-OH-loxapine (CYP1A2) and 7-OH-loxapine (CYP3A4 and CYP2D6), loxa-pine N-oxide by flavanoid monoamine oxidases (FMOs), and amoxapine, respectively. Due to extensive metabolism through various pathways, metabolic interactions should be minimal. It should be noted, however, that loxapine inhibits p-glycoprotein, although it is not a substrate for that transporter.¹¹

**Excretion**
Conjugated metabolites are renally eliminated and unconjugated via feces. The drug’s half-life ranges from six to eight hours.¹¹

**INDICATIONS AND DOSAGE**
Adasuve is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. To alleviate the risk of bronchospasm, Adasuve may be administered only to patients in a health care facility enrolled in the Adasuve Risk Evaluation and Mitigation Strategy (REMS) program. One 10-mg unit may be used once in a 24-hour period. After inhalation the patient must be monitored, including a physical exam with chest auscultation, for signs and symptoms of bronchospasm or other respiratory distress every 15 minutes for a minimum of one hour. Sites enrolled in the Adasuve REMS program must have immediate on-site access to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation).¹¹

Adasuve is contraindicated in patients with a history or current diagnosis of asthma, chronic obstructive pulmonary disease, emphysema, or other pulmonary disease associated with bronchospasm. Also, patients with acute respiratory signs or symptoms (wheezing, acute bronchospasms, and/or dyspnea) or currently receiving medications for airway diseases are contraindicated, as are patients with a known hypersensitivity to loxapine or amoxapine.¹¹

The efficacy data for clinical trials of Adasuve are summarized in Table 1, while data from trials of the drug’s pulmonary safety are summarized in Table 2.

**ADVERSE EFFECTS**
In three short-term (24-hour), randomized, double-blind, placebo-controlled clinical trials, 259 patients received Adasuve 10 mg. Based on pooled data from these trials, the most common adverse reactions were dysgeusia (14%), sedation (12%), and throat irritation (3%). Bronchospasms occurred in 0.8% of patients with no airway disease, 54% of patients with asthma (12% with placebo), and

### Table 2  Summary of Trials of Inhaled Loxapine's Pulmonary Safety

<table>
<thead>
<tr>
<th>Study subjects</th>
<th>Study design</th>
<th>Procedure summary</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>004-104</td>
<td>004-105</td>
<td>004-108</td>
<td></td>
</tr>
<tr>
<td>30 healthy nonsmokers ages 18–65</td>
<td>Randomized, double-blind, placebo-controlled, two-way crossover study</td>
<td>Participants received either inhaled placebo or 10 mg of inhaled loxapine in 2 doses within 24 hours with doses separated by 8 hours.</td>
<td>After 8 hours, 26.9% of participants in both the inhaled loxapine and placebo groups had a &gt; 10% reduction in FEV₁, FEV₁ reductions of ≥ 15% were experienced by 19.2% of those using inhalated loxapine compared with 3.8% using placebo. One patient had an FEV₁ reduction of ≥ 20% compared with none using placebo.</td>
</tr>
<tr>
<td>52 subjects with mild-to-moderate persistent asthma</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group study</td>
<td>Participants received either inhaled placebo or 10 mg of inhaled loxapine in 2 doses within 24 hours with doses separated by 10 hours.</td>
<td>Of patients receiving inhaled loxapine, 69% (n = 18) experienced severe AEs* compared with 12% (n = 3) receiving inhaled placebo. The most commonly reported AEs with loxapine: broncho-spasm (27%); chest discomfort (23%); wheezing (15%); and dyspnea (11.5%).</td>
</tr>
<tr>
<td>53 subjects with COPD</td>
<td></td>
<td>Of patients receiving inhaled loxapine, 58% (n = 15) experienced notable respiratory symptoms compared with 22% (n = 6) receiving inhaled placebo. The most commonly reported AEs with loxapine: dyspnea (11.5%); cough (11.5%); and wheezing (7.7%). There were no reports of bronchospasm.</td>
<td></td>
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</tbody>
</table>

**AE = adverse event; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second**

* Severe AE was defined as a ≥ 20% reduction in FEV₁ from baseline at first measurement, or use of rescue medication (bronchodilator).
19% of patients with COPD (11% with placebo). There were possible dose-related bronchospasms in patients with asthma (27% after one dose, 41% after a second dose). Other adverse effects include extrapyramidal symptoms (neck dystonia, 0.4%, and akathisia, 0.4%, versus 0% on placebo), tachycardia, hypotension, orthostatic hypotension, lightheadedness, and syncope.11 This medication is in pregnancy category C in all three trimesters.

**DRUG INTERACTIONS**

The concomitant use of central nervous system depressants such as loxapine with other agents, including sedatives, opioids, and antidepressants, may increase the risk of respiratory depression, hypotension, profound sedation, and syncope. Anticholinergic drugs, or those with anticholinergic properties, that are used with Adasuve may exacerbate glaucoma and urinary retention.11 Given the drug’s multiple pathways for metabolism, the risk for pharmacokinetic drug interactions is believed to be minimal. Further research is needed to study specific agents in combination with loxapine.

**COST**

The average wholesale price for a 10-mg package of Adasuve was $174 in August 2014.12

**CONCLUSION**

Adasuve consists of a novel inhalation delivery system combined with a well-studied and established antipsychotic agent. Although the system is relatively simple to self-administer, Adasuve requires cooperation from the patient. In some emergencies, this may not be an option when a patient is actively refusing medications. Clinical trials have established effectiveness for this route of delivery; however, clinicians should be mindful of the risks associated with it. If an institution meets the requirement for REMS authorization, Adasuve may be a less invasive or even patient-preferred option (as opposed to intramuscular routes) when emergency treatment of agitation is necessary.

**REFERENCES**


