

# Inhaled loxapine for agitation

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Approved by the FDA on December 21, 2012, loxapine inhalation powder is the newest agent commercialized for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults (*Table 1*).<sup>1,2</sup> Loxapine is a first-generation antipsychotic that garnered newfound interest because of its potential atypical properties.<sup>3</sup> Loxapine's reformulation allows for direct administration to the lungs, resulting in rapid absorption into systemic circulation. This formulation offers a different method to manage agitation, for which IM formulations of other antipsychotics have been approved.<sup>4</sup>

Inhaled loxapine is delivered using a handheld device that produces a thermally-generated condensation aerosol.<sup>5,6</sup> A single inhalation is sufficient to activate the controlled rapid heating (300 to 500°C in approximately 100 ms) of a thin layer of excipient-free loxapine on a metal substrate. Once vaporized, the medication cools down rapidly and aggregates into particles. The 1- to 3.5-micron aerosol particles of loxapine enter the respiratory track in <1 second. An estimated 11% of the emitted dose is deposited into the oropharyngeal region.<sup>7</sup>

## How it works

As with all antipsychotics, loxapine is an antagonist at the dopamine D2 receptor. However, loxapine also has clinically relevant serotonin-2A antagonism.<sup>3</sup> Pharmacologic effects for loxapine and its metabolites include biogenic amine transporter inhibitor activity, alpha adrenergic

**Table 1**

## Inhaled loxapine: Fast facts

<b>Brand name:</b> Adasuve
<b>Class:</b> Dibenzoxazepine antipsychotic
<b>Indication:</b> Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults
<b>FDA approval date:</b> December 21, 2012
<b>Availability date:</b> Third quarter of 2013
<b>Manufacturer:</b> Alexza Pharmaceuticals
<b>Dosing forms:</b> Single-dose inhaler, 10 mg
<b>Recommended dose:</b> 10 mg; only a single dose within a 24-hour period is recommended
<b>Source:</b> References 1,2

blocking effects, and histaminergic and muscarinic receptor affinity.<sup>3,8</sup>

## Clinical pharmacokinetics

In a phase I study of healthy volunteers, inhaled loxapine produced IV administration-type kinetics, with maximum plasma concentration achieved in approximately 2 minutes.<sup>6</sup> Plasma exposure to loxapine was dose-proportional. Half-life for the 5- and 10-mg doses was approximately 6 hours. In these patients, exposure to loxapine's metabolites as a percentage of exposure to the parent compound were 8.79% for 7-OH loxapine, 52.6% for 8-OH loxapine, and 3.96% for amoxapine (all produced as a result of metabolism via liver cytochrome P450 [CYP] enzymes CYP1A2, CYP2D6, and/or CYP3A4<sup>6</sup>). 7-OH loxapine has a 5-fold higher affinity for the dopamine D2

Reformulation allows for direct administration to the lungs, resulting in rapid absorption into systemic circulation

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**Clinical Point**

In the initial phase II trial, inhaled loxapine, 10 mg, but not 5 mg, was superior to placebo on the PANSS-EC at 2 hours

**Table 2**

**Summary of double-blind RCTs for inhaled loxapine vs inhaled placebo**

Study	Diagnosis	Loxapine		Placebo
		5 mg	10 mg	
Allen et al, 2011 <sup>9</sup> (Phase II)	Agitation associated with schizophrenia	n = 45	n = 41	n = 43
Lesem et al, 2011 <sup>10</sup> (Phase III)	Agitation associated with schizophrenia	n = 116	n = 113	n = 115
Kwentus et al, 2012 <sup>11</sup> (Phase III)	Agitation associated with bipolar I disorder (manic or mixed episode)	n = 104	n = 105	n = 105

<sup>a</sup>as measured by a CGI-I score of 1 or 2

BARS: Behavioral Activity Rating Scale; CGI-I: Clinical Global Impression Improvement Scale; NNT: number needed to treat; PANSS-EC: Positive and Negative Syndrome Scale Excited Component; RCTs: randomized controlled trials

receptor compared with loxapine, and may contribute to the drug’s clinical effect.<sup>6</sup>

Based on loxapine levels observed in the pharmacokinetic study,<sup>6</sup> loxapine is not extensively metabolized in the lungs. Peak plasma concentrations immediately after inhalation are higher than for oral loxapine, but concentration of loxapine and its metabolites after the initial distribution phase is similar to that of oral loxapine.<sup>6</sup> Loxapine and its metabolites are excreted through the kidneys.

**Efficacy**

Three efficacy studies were completed (Table 2)<sup>9-11</sup>; all were double-blind randomized controlled trials that compared inhaled loxapine, 5 or 10 mg, with placebo. Patients were required to be clinically agitated at baseline, with a score of ≥14 on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC)—which consists of the PANSS items of tension, excitement, hostility, uncooperativeness, and

poor impulse control; each item is rated from 1 (absent) to 7 (extreme)—and a score of ≥4 (moderate) on ≥1 item. Patients who were intoxicated or had a positive drug screen for psychostimulants were excluded. Lorazepam was allowed ≥2 hours after the study drug was administered. Change in the PANSS-EC was measured 10 minutes to 24 hours post-dose. The primary endpoint used to statistically test loxapine vs placebo was 2 hours post-dose.

In the initial phase II trial, loxapine 10 mg, but not 5 mg, was superior to placebo on the PANSS-EC at 2 hours.<sup>9</sup> The authors described the 5-mg dose effect size as intermediate between placebo and the 10-mg dose, suggesting a possible dose response relationship. The 10-mg dose did separate from placebo as early as 20 minutes post-dose. The small number of patients enrolled is a limitation of this trial, but this was addressed in studies in the phase III program, which were considerably larger. For each of the 2 phase III trials—1 for pa-



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Outcomes	Loxapine vs placebo NNT for response at 2 hours <sup>a</sup>	
	5 mg	10 mg
On the PANSS-EC score at 2 hours, loxapine, 10 mg, but not 5 mg, was superior to placebo. Loxapine, 10 mg, separated from placebo at 20 minutes, and control was sustained. On the CGI-I at 2 hours, both doses of loxapine were superior to placebo. Using the BARS, loxapine, 10 mg, was superior to placebo starting at 30 minutes and this effect was sustained. Dysgeusia was observed in 4% and 17% for loxapine, 5 mg and 10 mg, respectively, and 9% for placebo	4	3
On the PANSS-EC score and CGI-I at 2 hours, both doses of loxapine were superior to placebo. Loxapine separated from placebo at 10 minutes. Sustained control was observed over 24 hours. Dysgeusia was observed in 9% and 11% for loxapine 5 mg and 10 mg, respectively, and 3% for placebo	5	4
On the PANSS-EC score and CGI-I at 2 hours, both doses of loxapine were superior to placebo. Loxapine separated from placebo at 10 minutes. Sustained control was observed over 24 hours. Dysgeusia was observed in 17% for either loxapine 5 mg or 10 mg, respectively, and 6% for placebo	3	3

**Clinical Point**

Inhaled loxapine appears to reduce agitation equally well in patients with higher or lower levels of agitation at baseline

tients with schizophrenia<sup>10</sup> and the other for those with bipolar disorder (BD)<sup>11</sup>—both doses of loxapine were superior to placebo starting at 10 minutes post-dose. The number needed to treat (NNT) for response—as defined by a Clinical Global Impressions-Improvement score of much improved or very much improved—for loxapine vs placebo is included in *Table 2*.<sup>9-11</sup> NNT for other outcomes, such as reduction on the PANSS-EC by at least 40% from baseline, demonstrated similar results.<sup>12</sup> The lower the NNT, the stronger the effect size.<sup>13</sup> See the *Box (page 34)* for an explanation of NNT. NNTs in the range of 3 to 5 are comparable to other agents used to treat agitation.<sup>4</sup>

When examining each individual item on the PANSS-EC in each of the phase III trials, every item improved with treatment, starting 10 to 20 minutes after dosing.<sup>14</sup> Each item improved an average of 1 to 2 units from baseline over the first 2 hours post-dose. Moreover, inhaled loxapine ap-

pears to reduce agitation equally well in patients with higher or lower levels of agitation at baseline.

Another clinically relevant outcome is whether or not a patient required an additional dose or rescue medication within 24 hours. In the phase III schizophrenia trial,<sup>10</sup> 60.9% of patients randomized to loxapine, 10 mg, did not require an additional dose or rescue medication, compared with 54.4% and 46.1% for loxapine, 5 mg, and placebo, respectively. This yielded an NNT of 7 when comparing loxapine, 10 mg, with placebo.<sup>12</sup> In the BD study,<sup>10</sup> 61.5%, 41.3%, and 26.7% did not require an additional dose or rescue medication within 24 hours for loxapine, 10 mg, 5 mg, and placebo, respectively. In this study, the NNT for loxapine, 10 mg, vs placebo was 3.<sup>12</sup>

In general, there appears to be a dose response for efficacy with inhaled loxapine, and therefore the FDA approved the 10-mg dose.<sup>2</sup>

continued

**Box**

### What is number needed to treat?

Clinical trials produce a mountain of data that can be difficult to interpret and apply to clinical practice. When reading about studies you may wonder:

- How large is the effect being measured?
- Is it clinically important?
- Are we dealing with a result that may be statistically significant but irrelevant for day-to-day patient care?

Number needed to treat (NNT) and number needed to harm (NNH)—2 tools of evidence-based medicine—can help answer these questions. NNT helps us gauge effect size—or clinical significance. It is different from knowing if a clinical trial result is statistically significant. NNT allows us to place a number on how often we can expect to encounter a difference between 2 interventions. If we see a therapeutic difference once every 100 patients (an NNT of 100), the difference between 2 treatments is not of great concern under most circumstances. But if a difference in outcome is seen once in every 5 patients being treated with 1 intervention vs another (an NNT of

5), the result likely will influence day-to-day practice.

#### How to calculate NNT (or NNH)

What is the NNT for an outcome for drug A vs drug B?

$f_A$  = frequency of outcome for drug A

$f_B$  = frequency of outcome for drug B

$$NNT = 1 / [f_A - f_B]$$

By convention, we round up the NNT to the next higher whole number.

For example, let's say drugs A and B are used to treat depression, and they result in 6-week response rates of 55% and 75%, respectively. The NNT to encounter a difference between drug B and drug A in terms of responders at 6 weeks can be calculated as follows:

- Difference in response rates = 0.75 - 0.55 = 0.20
- NNT = 1 / 0.20 = 5.

**Source:** Adapted from Citrome L. Dissecting clinical trials with 'number needed to treat.' *Current Psychiatry*. 2007;6(3):66-71 and Citrome L. Can you interpret confidence intervals? It's not that difficult. *Current Psychiatry*. 2007;6(8):77-82

### Clinical Point

The most commonly encountered adverse event in patients receiving inhaled loxapine is dysgeusia

### Tolerability and safety

Combined safety results from phase III trials<sup>10,11</sup> as well as information about a phase I ECG QT interval study were presented in a poster.<sup>15</sup> Among 524 patients receiving loxapine vs 263 receiving placebo, there were no significant differences in the likelihood of experiencing any adverse event, a nervous system adverse event, sedation, sedation or somnolence, or sedation, somnolence or dizziness, when stratified by lorazepam rescue.<sup>16</sup> Adverse events that were more frequently encountered with both doses of loxapine (ie, 5 and 10 mg) than placebo are listed in *Table 3*,<sup>15</sup> along with the number needed to harm (NNH). The most commonly encountered adverse event was dysgeusia. The NNH of 10 for dysgeusia for loxapine, 10 mg, vs placebo means that for every 10 patients receiving inhaled loxapine, 10 mg, instead of inhaled placebo, you would encounter 1 additional case of dysgeusia. This contrasts with the NNT for

response of 4 and 3 for agitation associated with schizophrenia and BD, respectively. Therefore, one would encounter response more often than dysgeusia when comparing loxapine with placebo.

No important changes in the ECG QT interval after inhaled loxapine, 10 mg, were observed in a phase I study with healthy volunteers.<sup>15</sup> Difference from placebo in change from baseline for QTc was <10 ms at all post-dose times.

Additional details regarding overall safety and tolerability can be found in a previously published review.<sup>17</sup>

### Pulmonary safety

Because this product is inhaled, additional information on pulmonary safety was gathered.<sup>18,19</sup> Among 1,095 patients without active airways disease, 1 (0.09%) required treatment for post-treatment airway-related symptoms (bronchospasm). In the agitated patient population, the rate of airway ad-

Table 3

## Inhaled loxapine: Incidence of adverse events

Adverse event	Placebo (n = 220)	Loxapine			
		5 mg (n = 220)		10 mg (n = 218)	
	Rate	Rate	NNH vs placebo	Rate	NNH vs placebo
Dysgeusia	4%	13%	12	14%	10
Sedation or somnolence	8%	11%	34	10%	50
Oral hypoesthesia	0%	<0.5%	200	2%	50

NNH: number needed to harm  
Source: Reference 15

verse events was 0.4% of loxapine exposures among 524 patients, in which 6.7% had a history of asthma or chronic obstructive pulmonary disease (COPD). Others were likely to have some respiratory impairment because of a history of cigarette smoking, but they did not have active respiratory symptoms that required treatment because such patients were excluded from the trials.<sup>12</sup> Phase I spirometry-based studies also were completed in healthy nonsmoking volunteers, in patients with asthma, and in patients with COPD. No clinically relevant effects were observed in healthy volunteers, but in patients with asthma or COPD a reduction in forced expiratory volume was observed. In patients with asthma, rates of bronchospasm as an adverse event were 26.9% for loxapine vs 3.8% for placebo, for a NNH of 5.<sup>12</sup> Bronchospasm was not reported for patients with COPD receiving loxapine but was observed in 1 patient who received placebo. All airway adverse events in patients with asthma or COPD were mild or moderate. All respiratory signs or symptoms requiring treatment in the phase I asthma and COPD studies were managed with an inhaled bronchodilator.

Product labeling notes in a warning that inhaled loxapine can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest.<sup>2</sup> Therefore, inhaled loxapine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the

“ADASUVE REMS.” Enrolled health care facilities are required to have immediate, on-site access to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation). Inhaled loxapine is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung diseases associated with bronchospasm; acute respiratory signs or symptoms such as wheezing; current use of medications to treat airway diseases such as asthma or COPD; history of bronchospasm following inhaled loxapine treatment; or known hypersensitivity to loxapine and amoxapine.

Only a single dose within a 24-hour period is recommended. Before administration, patients should be screened for a history of pulmonary disease and examined (including chest auscultation) for respiratory abnormalities (eg, wheezing). After administration, patients require monitoring for signs and symptoms of bronchospasm at least every 15 minutes for  $\geq 1$  hour.

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## Clinical Point

The rate of airway adverse events was 0.4% among 524 agitated patients who were administered inhaled loxapine

Clinical Point

Inhaled loxapine is contraindicated in patients with a history of asthma, COPD, or other lung diseases associated with bronchospasm

Related Resource

• Dinh K, Myers DJ, Glazer M, et al. In vitro aerosol characterization of Staccato(®) Loxapine. *Int J Pharm.* 2011; 403(1-2):101-108.

Drug Brand Names

Haloperidol • Haldol	Loxapine • Loxitane
Lorazepam • Ativan	Loxapine inhalation powder • Adasuve

Disclosure

In the past 36 months, Dr. Citrome has engaged in collaborative research with or received consulting or speaking fees from Alexza Pharmaceuticals, Alkermes, AstraZeneca, Avanir Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, EnVivo Pharmaceuticals, Forest Pharmaceuticals, Genentech, Janssen, L.P., Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer Inc., Shire, Sunovion, and Valeant.

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Bottom Line

Inhaled loxapine is a possible alternative to parenteral injections of other antipsychotics for the rapid reduction of agitation in patients with schizophrenia or bipolar disorder. Because it essentially is self-administered under supervision, inhaled loxapine will not be a substitute for an injection during emergencies when a patient is actively refusing medication treatment. Regulatory restrictions on use may be an obstacle to inhaled loxapine's adoption on hospital formularies.