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Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO22/Room 4114
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock and Dr. Laughren:

These comments from Public Citizen's Health Research Group are being sent in response to New Drug Application (NDA) #22549, submitted by Alexza Pharmaceuticals, Inc., and considered by the Food and Drug Administration's (FDA) Psychopharmacologic Drugs Advisory Committee (PDAC) on December 12, 2011, for loxapine (Adasuve) inhalation powder (hereafter referred to as "inhaled loxapine") for the acute treatment of agitation associated with schizophrenia or bipolar I (mania) disorder in adults.

We strongly oppose FDA approval of the NDA for inhaled loxapine for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults because (1) there is no evidence from clinical trials that inhaled loxapine offers any significant or unique benefits over currently available FDA-approved treatments for acute agitation in such patients; and (2) there is unequivocal evidence that the drug — even after a single dose — can cause significant life-threatening pulmonary toxicity. As the FDA's own analysis demonstrated, there is no reasonable justification for approving this drug, and doing so would recklessly endanger patients' lives. The is no reason to believe that carving out a restricted approval for inhaled loxapine by limiting exposure to a single

dose under a risk evaluation and mitigation strategy (REMS) would be sufficient to prevent serious pulmonary toxicity from occurring and to protect public health. An FDA reviewer even recommended that, in order for the drug to be approved, the company should "**be required to submit adequate data on a formulation of the *Staccato* Loxapine product that demonstrates a lack of pulmonary toxicity** [emphasis added]**."**[1] Such data do not exist.

I. Background

Loxapine is a first-generation antipsychotic approved in 1975 for the treatment of schizophrenia. It currently is available only in capsule form for oral administration. Inhaled loxapine is delivered with a single-use, handheld drug device — the Staccato delivery system — intended to provide rapid systemic delivery by inhalation of a heat-generated aerosol of loxapine. Oral inhalation through the Staccato delivery system triggers the controlled rapid heating of a thin film of loxapine to form a drug vapor, which is then inhaled. The vapor condenses to aerosol-sized particles for delivery to the deep lung. This new dosage form and route of administration are intended to be used for the treatment of agitation associated with schizophrenia and bipolar I disorder. Three intramuscular forms of atypical antipsychotics are approved for this indication in the U.S.: (olanzapine [Zyprexa], ziprasidone [Geodon], and aripiprazole [Abilify]). Loxapine inhalation powder, if approved, would be the first inhaled form of an antipsychotic for this use.[2]

Alexza Pharmaceuticals is seeking approval for inhaled loxapine at a dose of 5 mg or 10 mg as frequently as every two hours as needed, up to a maximum of three doses per day.[3]

The sponsor submitted an initial NDA on December 11, 2009. On October 8, 2010, the FDA issued a complete response letter because of serious concerns regarding pulmonary toxicity. The sponsor subsequently resubmitted the NDA with revisions.

II. The risks of inhaled loxapine: serious pulmonary toxicity

Given the route of delivery, the FDA was reasonably concerned about the potential pulmonary toxicity of inhaled loxapine. Therefore, the agency directed Alexza Pharmaceuticals to conduct phase 1 pulmonary toxicity studies of inhaled loxapine in healthy subjects (trial 004-104), patients with asthma (trial 004-105), and patients with chronic obstructive pulmonary disease (COPD) (trial 004-108).[4] These studies demonstrated highly clinically significant drug-related abnormalities in pulmonary function test results in all three groups and high rates of pulmonary adverse events, especially in subjects with asthma and COPD, providing clear evidence of serious, potentially life-threatening pulmonary toxicity caused by the drug.

Moreover, the phase 3 pivotal clinical trials and other phase 1 and 2 trials of inhaled loxapine in agitated subjects and healthy subjects failed to provide useful information on adverse events that would be relevant to the intended target patient populations

because (1) these trials excluded subjects with clinically significant acute or chronic pulmonary disease — such as clinically apparent asthma or COPD — and most trials also excluded subjects who were active smokers, and (2) there is a high prevalence of smoking and, as a result, pulmonary diseases such as COPD in patients with schizophrenia and bipolar I disorder.

A. Pulmonary toxicity study in healthy subjects (trial 004-104)

Trial 004-104 was a single-center, randomized, placebo-controlled, two-period crossover trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as two doses eight hours apart on the same day, in healthy subjects. A total of 30 healthy nonsmoking subjects 18-65 years of age were administered a placebo or loxapine with a washout of at least four days between treatments. Subjects were required to have normal pulmonary function at baseline, defined as forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) ≥85% predicted and room air oxygen saturation ≥95% by pulse oximetry, and no history of asthma, COPD, or other pulmonary disease.[5]

Table 1 presents a responder analysis showing the maximum FEV1 decrease from the same period baseline after either dose of the placebo or loxapine in healthy subjects. One-third of healthy subjects had a clinically significant decrease in FEV1 following exposure to either loxapine or placebo, with the most severe decreases occurring much more frequently following loxapine exposure.

Table 1: Trial 004-104: Maximum FEV1 decrease from same period baseline after either dose (safety population)[6]

Maximum FEV1 decrease	**Placebo N=29 n (%)**	**Loxapine 10 mg N=27 n (%)**
≥ 10%	10 (34.5)	9 (33.3)
≥ 15%	1 (3.4)	6 (22.2)
≥ 20%	0	2 (7.4)

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

In commenting on these results, Dr. Anya Harry, an FDA medical reviewer in the Center for Drug Evaluation and Research's (CDER) Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) who analyzed the pulmonary safety data in the initial NDA submission for inhaled loxapine, stated the following in her August 20, 2010 review memorandum:[7]

> *[I]t is notable that in a "responder analysis" there were more patients with significant drops in FEV1 in the loxapine group than in the placebo group, suggesting that loxapine induces some degree of airway hyperresponsiveness in a subgroup of normal people* [italics in the original].

Dr. Robert L. Levin, the FDA cross-discipline team leader, noted the following regarding the results of trial 004-104 in his September 30, 2010 review memorandum for the initial NDA submission for inhaled loxapine:[8]

> The primary findings from pulmonary testing were decreases in forced expiratory volume in one second (FEV1). A significant decrease in FEV1 indicates that there is an obstruction to air escape. **A decrease in FEV1 of > 10% is considered clinically significant** [emphasis added]. In healthy subjects, 27% had a decrease > 10% in both the Staccato Loxapine and the Staccato placebo groups. This suggests that both delivery of loxapine to the lung and the use of the Staccato device may play a role in the development of pulmonary toxicity and bronchospasm. In healthy subjects, 19% treated with Staccato Loxapine and 4% treated with Staccato placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with Staccato Loxapine had a decrease in FEV1 > 20%. To put these data in perspective, Dr. Harry notes that standard bronchoprovocation tests cause decreases in FEV1 of 10-20%.

Finally, Dr. Theresa M. Michele, clinical team leader in DPARP, stated the following in her November 2, 2011 review memorandum regarding the resubmission of the NDA for inhaled loxapine:[9]

> [I]f the results are evaluated by maximal FEV1 decrease (responder analysis), approximately one third of patients in the safety population had clinically important FEV1 decreases of ≥10% …, suggesting that **both inhaled loxapine and placebo given via the Staccato device may cause some degree of bronchospasm, even in healthy subjects** … [emphasis added].
>
> The sponsor explains these decreases as sedative effects, normal variability, and incomplete effort on the part of the subjects. The FEV1/FVC ratio was inconsistently decreased from baseline, and did not decrease out of the normal range, arguing against bronchospasm. However, in normal subjects, early obstructive changes may be represented by changes in the small airways that do not affect this ratio. Further, while some degree of variability and diurnal variation is expected, changes >15% are unusual.

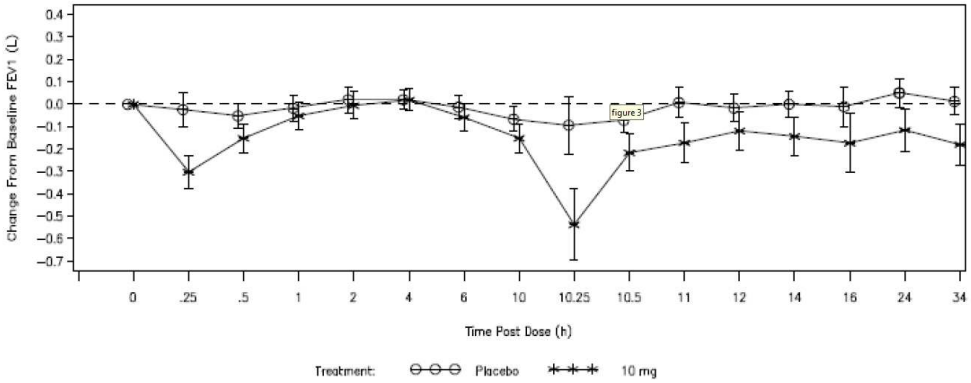
B. Pulmonary toxicity study in patients with mild to moderate persistent asthma (trial 004-105)

Trial 004-105 was a multicenter, randomized, placebo-controlled, parallel group trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as two doses 10 hours apart on the same day, in 52 patients with mild to moderate persistent asthma. Patients were required to have a pre-bronchodilator FEV1 ≥60% predicted, have a history of FEV1 reversibility, and be on a stable asthma drug regimen for at least two weeks prior to dosing. Patients with ≥10-pack-year smoking history were excluded. Fifty-two patients were randomized into the trial and 51 completed it. Of the 52 treated patients, only 42 received both planned doses of study treatment. Ten patients (nine in

the loxapine group and one in the placebo group) received only one dose, primarily due to a decrease in FEV1 ≥ 20% and respiratory adverse events.[10]

Figure 1 and table 2 demonstrate the effect of inhaled loxapine and placebo on FEV1 in the asthmatic subjects. As shown in figure 1, there was a marked decrease in FEV1 immediately after dosing in the loxapine-treated group. Decreases were greater after the second dose of loxapine, given 10 hours after the first dose, and the group mean did not return to baseline after the second dose.[11]

Figure 1: Trial 001-105: FEV1 change from baseline by treatment (spirometry population)[12]



Note: Patients with a ≥20% decrease in FEV1 did not receive a second dose of study drug and are not included in the curves beyond hour 10.

The results from the responder analysis, presented in table 2, show that 85% of loxapine-treated subjects had a decrease in FEV1 of ≥10%, and 42% had a decrease of ≥20%. The FDA review noted that the true FEV1 nadir is unknown because all patients with a ≥20% decrease in FEV1 received albuterol.[13] It is also important to note that even a single dose of inhaled loxapine had significant pulmonary toxicity as assessed by FEV1 measurements.

Table 2: Trial 004-105: Maximum FEV1 decrease from baseline (spirometry population)[14]

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

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

Table 3 provides a summary of adverse events related to airways in trial 004-105. The most common airway adverse events in subjects receiving inhaled loxapine were bronchospasm (27%), chest discomfort (23%), wheezing (15%), and dyspnea (shortness of breath) (12%).

Table 3: Adverse events related to airways (safety population) — trial 004-105[15]

Adverse Event, n (%)	*Staccato* Placebo (N=26)	*Staccato* Loxapine (N=26)
No. (%) of subjects with any airway AE	3 (11.5%)	14 (53.8%)
Bronchospasm	1 (3.8%)	7 (26.9%)
Chest discomfort	2 (7.7%)	6 (23.1%)
Wheezing	0	4 (15.4%)
Dyspnea	0	3 (11.5%)
Cough	0	1 (3.8%)
Throat tightness	0	1 (3.8%)
Forced expiratory volume decreased	0	1 (3.8%)

Note: All AEs presented in this study report were treatment emergent. Subjects with more than 1 occurrence of a specific AE are counted only once.

Dr. Francis E. Becker, the FDA primary clinical reviewer, noted the following in his November 8, 2011 review of the revised NDA submission for inhaled loxapine:[16]

> In subjects with asthma (Trial **004-105**), eighteen (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs or symptoms, defined as the forced expiratory volume in the first second (FEV1) decrease from baseline of ≥20%, an airway [adverse event (AE)], or use of rescue (bronchodilator) medication.

C. Pulmonary toxicity study in patients with mild to severe COPD (trial 004-108)

Trial 004-108 was a multicenter, randomized, placebo-controlled, parallel group trial assessing the pulmonary safety of 10 mg inhaled loxapine, administered as two doses 10 hours apart on the same day, in 53 patients with mild to severe COPD. Patients were required to have a >15-pack-year history of smoking, a post-bronchodilator FEV1 ≥40% predicted, and an FEV1/FVC ratio of <0.70, and be on a stable COPD drug regimen for at least two weeks prior to dosing. Of the 52 treated patients, 45 received both planned doses of study treatment. Eight patients (seven in the loxapine group and one in the placebo group) received only one dose, primarily due to a decrease in FEV1 ≥20% and respiratory adverse events.[17]

Similar to the asthma subjects, there was a decrease in FEV1 immediately after dosing in the loxapine-treated group, although the amount of change was less than in the asthma subjects.[18] The FDA review noted the following regarding this difference:[19]

> This is typical for bronchoreactive effects in a COPD population, in which there is a greater degree of fixed obstruction and less reactive component. In addition, this population has a lower baseline lung function than the asthma population, so smaller changes are expected.

The results from the responder analysis, presented in table 4, show that 80% of loxapine-treated subjects had a decrease in FEV1 of ≥10%, and 40% had a decrease of ≥20%. The FDA review noted that the true FEV1 nadir is unknown because all patients with a ≥20% decrease in FEV1 received albuterol.[20] In addition, there were a large number of patients with decreases in the placebo group, suggesting that COPD patients may be more susceptible to changes in lung function due to the hot air from the device.[21] Finally, the FDA reported that there was no difference in percentage of patients with FEV1 drops when analyzed by smoking status (current versus former smokers).[22]

Again, it is also important to note that even a single dose of inhaled loxapine resulted in significant pulmonary toxicity as assessed by FEV1 measurements.

Table 4: Trial 004-108: Maximum FEV1 decrease from baseline (spirometry population)[23]

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

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

Table 5 provides a summary of adverse events related to airways in trial 004-108. The most common airway adverse events in subjects receiving inhaled loxapine were dyspnea (12%), cough (12%), and wheezing (8%).

Table 5: Adverse events related to airways (safety population) – trial 004-108[24]

Adverse Event, n (%)	***Staccato* Placebo** (N=27)	***Staccato* Loxapine** (N=26)
No. (%) of subjects with any airway AE	3 (11.1%)	5 (19.2%)
Dyspnea	1 (3.7%)	3 (11.5%)
Cough	0	3 (11.5%)
Wheezing	0	2 (7.7%)
Forced expiratory volume decreased[a]	0	1 (3.8%)[a]
Pulmonary congestion	0	1 (3.8%)
Bronchospasm	1 (3.7%)	0
Productive cough	1 (3.7%)	0

Note: All AEs presented in this study report were treatment emergent. Subjects with more than 1 occurrence of a specific AE are counted only once.

D. Pulmonary adverse events in other trials for inhaled loxapine, including the pivotal clinical trials (trials 004-301 and 004-302)

The FDA review noted the following regarding the occurrence of pulmonary adverse events in other trials for inhaled loxapine:[25,26]

> In the controlled studies in agitated patients population (subjects from the 2 pivotal trials, 004-301 and 004-302, and the phase 2 proof of concept trial, 004-201), the most frequently reported respiratory system AEs in loxapine-treated subjects versus placebo-treated subjects were throat irritation (~2% vs. 0.4%), pharyngeal hypoaesthesia (0.6% vs. 0%), and wheezing (0.4% vs. 0%). The two subjects with AEs of wheezing did not require treatment. Bronchospasm was reported for one subject in the Staccato Loxapine 10 mg group in Trial 004-301, resulted in early discontinuation, and required treatment with a bronchodilator. All the respiratory AEs were mild to moderate …
>
> In the trials of healthy volunteers, there were no incidences of wheezing or bronchospasm; however, a high incidence of cough (~7% of loxapine-treated subjects compared to ~2% of placebo-treated subjects) was noted, which may be suggestive of underlying bronchospasm.
>
> Thus, although a particularly high incidence of respiratory adverse events was not found in the pivotal trials or in the Phase 1 and 2 trials, it is noteworthy that subjects with clinically significant acute or chronic pulmonary disease, such as clinically apparent asthma, chronic bronchitis, or emphysema, were excluded from these trials. In the trials of healthy volunteers (**004-101**, **004-103**, **004-104**, and **004-107**), subjects who reported regular tobacco use within the last year were excluded. The only exceptions were in Trial **004-102**, in which subjects with a history of asthma or chronic obstructive lung disease were excluded, and in Trial **004-106**, a pharmacokinetic study of healthy smokers compared to nonsmokers, but in this trial subjects were excluded for FEV1 < 80% of predicted or FVC < 80% of predicted.

E. Factors that would heighten the risk of pulmonary toxicity in the intended target patient populations

The FDA reviewers repeatedly highlighted multiple factors that heighten the risk of serious pulmonary adverse events in the intended target patient populations for inhaled loxapine. These factors include:

- A high prevalence of smoking and smoking-induced pulmonary disease in the intended target patient populations;
- Inability of health care providers to effectively screen patients for prior history of smoking and pulmonary disease because of acute agitation;
- Inability of patients to use the inhalation device effectively because of acute agitation; and

- Failure of patients to manifest, or health care providers to detect, signs and symptoms of severe drug-induced bronchospasm and airway obstruction because of psychosis, agitation, or sedation following dosing.

For example, Dr. Levin, the FDA cross-discipline team leader, noted the following in his September 30, 2010 review memorandum for the initial NDA submission for inhaled loxapine:[27]

> Additional factors could contribute to an excessive risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high rate of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline. As demonstrated in the pulmonary safety studies, exposure to Staccato Loxapine can result in acute obstructive exacerbations requiring rescue bronchodilator treatment in patients with baseline obstructive disease. Another concern is that acutely agitated patients with schizophrenia or bipolar disorder may be incapable of providing an accurate history of pulmonary disease. Similarly, healthcare professionals may not be able to perform an adequate respiratory examination during an acute episode of agitation. Moreover, sedation from Staccato Loxapine could obscure respiratory signs and symptoms. Finally, dosage and administration of proposed labeling indicates that Staccato Loxapine could be administered every 2 hours up to 3 times, which would allow repeat dosing prior to recovery of FEV1.

Likewise, Dr. Becker, the FDA primary clinical reviewer, in summarizing the concerns raised in the agency's complete response action letter to the initial NDA submission for inhaled loxapine, noted the following in his November 8, 2011 review of the revised NDA submission:[28,29]

> The high rate of smoking in patients with Schizophrenia and Bipolar Disease has been well-documented. In one study, Hughes et al (American Journal of Psychiatry 1986, 143: 993-997) reported that the prevalence of smoking among psychiatric outpatients was significantly higher than among either local or national population-based samples (52% versus 30% and 33%) and that smoking was especially prevalent among patients with Schizophrenia (88%) or Mania (70%) and among the more severely ill patients. In another study, Goff et al (American Journal of Psychiatry 1992, 149: 1189-1194) reported that 74% of a group of schizophrenic outpatients smoked. Therefore, a high rate of asthma and COPD in the intended treatment population would be expected, and it is likely that excluding subjects with clinically significant pulmonary disease from the efficacy trials (004-201, 004-301, and 004-302) trials and subjects who reported regular tobacco use from many of the Phase 1 trials resulted in a better pulmonary safety profile than would be expected in the target population …
>
> It is unlikely that schizophrenic or bipolar patients presenting with acute agitation would be able to give a reliable medical history. In a case-matched, retrospective review, Roberts et al. (Family Practice; 24: 34-40) demonstrated that patients

> with Schizophrenia were less likely than asthma controls to have smoking status noted and in general were less likely to receive some important general health checks than patients without Schizophrenia. Thus, it would be extremely difficult for practitioners to exclude patients at risk for airway adverse reactions (i[.]e[.], patients with asthma or COPD), especially in an emergency room setting where the patient's medical history may not be known or readily available. In many settings (e.g., a psychiatric inpatient ward or a psychiatrist's office), early recognition and prompt treatment of an airway adverse reaction in an already agitated patient may not be feasible, and appropriate rescue medication may not be readily available.

Finally, Dr. Becker provided the following remarks regarding the pulmonary safety concerns about inhaled loxapine in the conclusions of his November 8, 2011 review of the revised NDA submission for inhaled loxapine:[30]

> As previously noted, there is a very high rate of smoking in patients with schizophrenia and bipolar disorder. Therefore, a high rate of asthma and COPD would be expected. However, acutely agitated schizophrenic or bipolar patients presenting to an emergency room or other facility may be uncooperative, psychotic, and severely disorganized. In some cases, they may need physical restraint. Such patients may be unable to give a reliable medical history and, in an emergency setting, medical records may not be readily available. In addition, these patients may be unable or unwilling to follow directions for use of ADASUVE. Furthermore, healthcare providers may have difficulty performing an adequate physical examination on an acutely agitated, disorganized patient. Therefore, even if the at-risk population can be fully characterized, a proportion of high risk patients will not be identified and will receive ADASUVE.
>
> It may be difficult to monitor patients for early signs and symptoms of bronchospasm post-dose. Psychotic and agitated patients who develop respiratory symptoms may not be able to notify healthcare personnel in a timely manner, and respiratory distress may be confused with acute agitation to the casual observer. In addition, the sedating effect of *Staccato* Loxapine may also mask respiratory signs and symptoms while causing further respiratory suppression.

III.The potential benefits of inhaled loxapine are limited

The clinical efficacy of inhaled loxapine was assessed in two phase 3, randomized, placebo-controlled clinical trials, one in agitated subjects with schizophrenia and the other in agitated subjects with bipolar I disorder. Up to three doses of inhaled loxapine (5 mg or 10 mg) were administered at intervals of at least two hours. In each trial, both the 5- and 10-mg doses met the primary efficacy endpoints (change in Positive and Negative Symptom Scale, Excited Component score from baseline to two hours after the first dose, active versus placebo) and the key secondary endpoint (Clinical Global

Impression — Improvement Scale score two hours after the first dose, active vs. placebo).[31]

Although inhaled loxapine was shown to be superior to the placebo in these clinical trials, FDA reviewers questioned whether conclusions about efficacy could be extrapolated to the real-world setting — particularly the emergency room setting — in which this drug would be used. For example, Dr. Becker, the FDA primary clinical reviewer, noted the following in his September 17, 2010 review of the initial NDA submission for inhaled loxapine:[32]

> However, most patients [enrolled in the phase 3 clinical trials] were recruited from referrals in the community, undergoing device training and extensive pre-treatment screening (up to 2 days or more in Trial **004-301**, and up to 24 hours in Trial **004-302**). No patients were recruited from psychiatric emergency rooms, yet psychiatric emergency rooms would likely be a common setting for use of *Staccato* Loxapine if it is approved. Patients presenting to a psychiatric emergency room may be less cooperative and are less likely to have an established relationship with the health care provider. Under such circumstances, it is unclear if device training would be as effective as it was in the pivotal trials and if *Staccato* Loxapine could be effectively administered.

Dr. Becker also noted the following in his November 8, 2011 review of the revised NDA submission for inhaled loxapine: [33]

> *[I]t is apparent that patients in the pivotal trials underwent fairly extensive training in use of the [Staccato delivery system] device. At baseline, a plastic model of the device was available, and patients apparently had up to 1 hour for repeat device training prior to study drug administration. Acutely agitated schizophrenic or bipolar patients presenting to an emergency room or other acute care center where prior screening is not practical and where the goal is to treat the agitation as soon as possible may not respond as well to device training* [italics in original].

FDA reviewers also questioned whether inhaled loxapine offered any advantages over current FDA-approved treatments for agitation in patients with schizophrenia or bipolar I disorder.

For example, Dr. Becker, in summarizing the concerns raised in the agency's complete response action letter to the initial NDA submission for inhaled loxapine, noted the following in his November 8, 2011 review of the revised NDA submission:[34]

> **Appropriate, safer alternatives to Staccato Loxapine have already been approved** [emphasis added]. Intramuscular medication (aripiprazole, ziprasidone, and olanzapine) is available for treatment of acute agitation associated with Bipolar disorder or Schizophrenia. These medications have a reasonably rapid onset and have a safety profile similar to loxapine. However,

> the possibility of potentially serious respiratory adverse events is greatly decreased with intramuscular administration of these medications.

Furthermore, Dr. Laughren noted the following in his November 14, 2011 memorandum to PDAC members regarding inhaled loxapine:[35]

> What has not yet been established, however, is how this product compares in effectiveness to the 3 intramuscular forms of atypical antipsychotics that are already approved for this indication in the US. Although the sponsor has provided some cross study comparisons to try to make the case that Staccato Loxapine for Inhalation may work faster than these other products, there has not yet been a head-to-head comparison of Staccato Loxapine with these other products, either alone, or in combination with benzodiazepines, as these products are often used in practice.

In summary, there is no evidence from clinical trials that inhaled loxapine offers any significant or unique benefits over currently available FDA-approved treatments for acute agitation in patients with schizophrenia or bipolar I disorder. Moreover, inhaled loxapine is likely to be less effective in the real-world setting than in the carefully controlled setting of the two pivotal clinical trials of this drug.

IV. Overall risk-benefit assessment

The overall risk-benefit assessment for inhaled loxapine is very straightforward.

With respect to risks, there is overwhelming evidence from the phase 1 pulmonary safety studies that inhaled loxapine, even after a single dose, causes significant pulmonary toxicity that results in a high rate of very clinically significant bronchospasm and airway obstruction. Moreover, given their clinical characteristics, the intended target patient populations are particularly predisposed to developing serious pulmonary toxicity following exposure to the drug.

In contrast, safer FDA-approved alternative treatments for agitation in patients with schizophrenia or bipolar I disorder are currently available, and there is no evidence from clinical trials that inhaled loxapine offers any significant or unique benefits over these alternatives. Moreover, inhaled loxapine is likely to be less effective in the real-world setting than in the carefully controlled setting of the two pivotal clinical trials for this drug.

Therefore, the risks of this drug greatly outweigh its limited benefits. The FDA obviously reached this same conclusion — the only possible conclusion — when it issued a complete response letter to Alexza Pharmaceuticals' initial NDA submission for inhaled loxapine.

For example, Dr. Becker, the FDA primary clinical reviewer, made the following conclusions and recommendations in his September 17, 2010 review of the initial NDA submission for inhaled loxapine:

> ***1.1 Recommendation on Regulatory Action***
>
> Based on the data provided, I recommend a Complete Response action be taken for Staccato Loxapine for Inhalation in the treatment of acute agitation associated with Schizophrenia or Bipolar Disorder. **In an acute situation, *Staccato* Loxapine may prove difficult to use, and the risk of serious respiratory adverse events associated with its use in the target population is very high. Moreover, appropriate, alternative medication is available** [emphasis added] …[36]
>
> ***1.3 Recommendation for Postmarket Risk Evaluation and Mitigation Strategies***
>
> From a clinical perspective, **safety issues associated with *Staccato* Loxapine are numerous and profound. REMS would not be adequate or sufficient to address these issues** [emphasis added].[37]

Likewise, Dr. Harry, an FDA medical reviewer in DPARP who analyzed the pulmonary safety data in the initial NDA submission for inhaled loxapine, summarized DPARP's conclusions in her August 20, 2010 review memorandum:[38]

> Based on these findings, DPARP recommends that the risk benefit profile of Staccato Loxapine use in a psychiatric population who may have known or unknown pulmonary comorbidities may not be favorable for approval. The acute pulmonary toxicity seen in the patients with known pulmonary disease treated with Staccato Loxapine was clinically significant. We are particularly concerned regarding the safety of Staccato Loxapine in patients whose pulmonary history may not be known during treatment for acute agitation as well as the ability of health care or home personnel to recognize and respond to post-dosing respiratory distress.

Dr. Levin, the FDA cross-discipline team leader, stated the following in his September 30, 2010 review memorandum regarding the initial NDA submission for inhaled loxapine:

> Anya Harry, M.D., Ph.D. performed the review of the pulmonary toxicity studies … Dr. Harry notes that there are highly clinically significant findings of drug-related abnormalities in pulmonary function test results in the studies. The abnormalities were particularly marked and clinically significant in patients with asthma and COPD. In addition, there were clinically significant respiratory signs and symptoms including bronchospasm, dyspnea, wheezing, chest discomfort, and cough). Furthermore, a significant proportion of asthma and COPD patients

> required rescue treatment with bronchodilator medication. As a result of these significant pulmonary safety findings, Dr. Harry has recommended a complete response action**. I agree with Dr. Harry's conclusions and recommendations. The pulmonary safety findings are highly clinically significant. My opinion is that treatment with Staccato Loxapine would not be reasonably safe in patients with schizophrenia, who have an extremely high prevalence of chronic smoking along with a relatively high risk of pulmonary disease burden** [emphasis added] …[39]
>
> **11.2 Safety Review** Francis Becker, M.D conducted the safety review. Dr. Becker has concluded that treatment with Staccato Loxapine in patients with schizophrenia or bipolar [disorder] would not be reasonably safe, due to the serious pulmonary function test abnormalities…. In addition, a significant proportion of subjects in the pulmonary safety studies developed clinically significant respiratory symptoms requiring rescue treatment with bronchodilator medication in some cases. Patients with schizophrenia and bipolar disorder have a high rate of smoking; thus, they are at relatively high risk of developing chronic obstructive disease. Thus, these patient populations would have a relatively high risk of developing pulmonary toxicity if exposed to *Staccato* Loxapine for Inhalation. I agree with Dr. Becker's conclusion. **In my opinion, treatment with *Staccato* Loxapine would not be reasonably safe, due to the pulmonary toxicity findings in the clinical program. In general[,] I agree with Dr. Becker's conclusions regarding the overall safety analysis** [emphasis added].[40]

Dr. Levin made the following concluding recommendation:

> **16.1 Recommended Regulatory Action**
>
> I recommend a Complete Response action, due to the considerable risk of pulmonary toxicity with use of Staccato Loxapine for Inhalation. Three pulmonary safety studies demonstrated that there were significant abnormalities in pulmonary function test parameters for healthy subjects, subjects with asthma, and subjects with COPD. The abnormalities were marked in the asthmatic and COPD patients.[41]

Dr. Levin also advised that the FDA's regulatory action letter in response to the initial NDA submission include the following comments:[42]

> **In our opinion, labeling or a …REMS …would not provide a reasonable degree of safety regarding the risk of pulmonary toxicity in the intended population** [emphasis added].
>
> <u>Requirements for Resolving the Deficiencies</u>:

> **You would be required to submit adequate data on a formulation of the *Staccato* Loxapine product that demonstrates a lack of pulmonary toxicity** [emphasis added].

Finally, Dr. Laughren, in his October 7, 2010 memorandum presenting the Division of Psychiatry's recommendation for a complete response action for the initial NDA submission for inhaled loxapine, stated the following conclusions and recommendations:[43]

> I agree with the review team that the deficiencies for this application are sufficient to justify a [complete response] action at this time. **Primary clinical concerns include both the pulmonary safety issues, and the fact that this product has not been tested adequately in the typical emergency room setting**, i.e., naïve patients with a less than optimal medical history, and the population most likely to be administered this product [emphasis added]. **As Dr. Becker has noted, there are alternative products available for the treatment of acute agitation in schizophrenia** [emphasis added].

However, rather than conducting additional clinical trials testing inhaled loxapine in the typical emergency room setting or developing a reformulation of inhaled loxapine that demonstrates a lack of pulmonary toxicity — a proposed requirement that apparently was not included in the FDA's final complete response action letter for the initial NDA submission for inhaled loxapine — Alexza Pharmaceuticals submitted a revised NDA for the same formulation of inhaled loxapine without presenting any additional evidence from clinical testing to demonstrate that the drug has a favorable risk-benefit profile. The sponsor instead sought to allay the FDA's concerns about severe pulmonary risk posed by inhaled loxapine by proposing additional warnings in the drug's label and a REMS. Given the risk-benefit profile, such an approach would be unacceptable.

Indeed, the FDA's reviews of the revised NDA for inhaled loxapine continue to highlight the unacceptable risk-benefit profile of inhaled loxapine.

Dr. Michele, clinical team leader in DPARP, again summarized her division's concerns about the serious pulmonary toxicity caused by inhaled loxapine in her November 2, 2011 review memorandum as follows:[44,45]

> **5. Risk/Benefit Assessment**
>
> ***5.1. Pulmonary risks***
>
> **From a pulmonary standpoint, the risk of acute bronchospasm with inhaled loxapine is clear, particularly in patients with underlying airway hyperresponsiveness such as those with asthma and COPD** [emphasis added]. Although bronchospasm did not lead to serious outcomes such as hospitalization, intubation, or death in the clinical trials performed with inhaled loxapine, the safety database is limited in size and there are a number of factors

related to the proposed patient population and therapeutic effects of the drug that raise concerns of increased risk of serious events. These include:

- Patients with schizophrenia and bipolar disorder have a high prevalence of smoking, which increases the risk of airway disease.
- Patients with acute agitation may be unable to give a reliable history of airway disease and be uncooperative with physical examination, making screening these patients out prior to administration difficult. In the Phase 2 and 3 clinical trials, patients with clinically apparent asthma and COPD were ineligible for the trial and were screened up to two weeks prior to enrollment for schizophrenia patients and up to 24 hours prior to enrollment for bipolar patients. Patients were not necessarily in an agitated state during screening. Even so, four patients had clinical symptoms of bronchospasm, and one was discontinued due to acute wheezing that required albuterol.
- Patients with acute agitation may be seen in an emergency setting in which practitioners familiar with the patient's history and healthcare records are unavailable. This also limits the ability to screen out patients with underlying airway disease.
- Many healthcare facilities in which patients with acute agitation are cared for, such as psychiatry clinics or inpatient psychiatric facilities, do not routinely keep materials or staff on hand to treat acute bronchospasm (albuterol nebulization, IV corticosteroids) or perform advanced airway management (intubation and mechanical ventilation). This increases the risk of a serious outcome for the individual patient if a respiratory adverse event occurs.
- Risk factors for death from asthma include low socioeconomic status or inner-city residence, illicit drug use, major psychosocial problems, other chronic lung disease, and chronic psychiatric disease.
- Inhaled loxapine is a sedative. Patients who are sedated may be less likely to report symptoms of bronchospasm and may have less evidence of wheezing on physical examination due to more shallow breathing.
- Not all patients may recognize symptoms of bronchospasm. Even patients with known asthma may perceive the severity of airflow obstruction poorly. This was evidenced in clinical trials with inhaled loxapine in which some patients with a FEV1 decrease of >20% were asymptomatic.
- Monitoring for acute bronchospasm with pulse oximetry is unlikely to be helpful because oxygenation is generally maintained until respiratory failure ensues.
- The proposed dosing for inhaled loxapine is as frequently as every 2 hours for up to three 10 mg doses. No spirometry safety data are available at this dosing frequency or number of doses. Pulmonary safety trials in asthma and COPD patients were performed with dosing every 10 hours for 2 doses, and there was evidence of worsened airflow obstruction after the second dose. Further, in the asthma trial, FEV1 did not return to baseline as late as 14 hours after the second dose, increasing the risk of severely worsened lung function if an additional dose were given prior to recovery.

> **Based upon the clinical trial data with evidence of bronchospasm, especially in patients with underlying respiratory conditions, and the additional considerations above, DPARP has concerns for bronchospasm and the potential for respiratory decompensation, including respiratory arrest, with inhaled loxapine** [emphasis added].

Dr. Becker, the FDA primary clinical reviewer, responding to Alexza Pharmaceuticals' arguments downplaying the FEV1 findings in the phase 1 pulmonary toxicity safety trials of inhaled loxapine, noted the following in his November 8, 2011 review of the revised NDA submission for the drug:

> *It is not surprising that subjects with COPD had smaller group mean decreases in FEV1, fewer airway AEs, and less need for rescue medication compared to subjects with asthma. By definition, subjects with COPD, unlike subjects with asthma, have chronic and less reversible airway disease.* ***However, it is important to realize that small decreases in FEV1 in patients with COPD, who already have respiratory compromise, may result in significant increases in morbidity*** [italics in original, bold added for emphasis].[46]
>
> *As previously noted, a decrease in FEV1 is an early sign of respiratory compromise. The patient may not develop signs and symptoms (e.g., wheezing, decreases in O2 saturation, increased respiratory rate) until much later. In the controlled setting of the clinical trials where otherwise healthy patients are carefully monitored and frequent spirometry assessments are done, early diagnosis and treatment of respiratory adverse reactions is possible. In a clinical setting, where patients with schizophrenia or bipolar disorder are presenting with acute agitation and in many cases are psychotic, uncooperative, and severely disorganized and where frequent spirometry assessments are not possible, it may be much less likely that signs and symptoms of pulmonary toxicity are identified in a timely fashion, increasing the possibility of less favorable outcomes compared to the outcomes in the clinical trials. The sedation effect of Staccato Loxapine may further compromise the patient's ability to report respiratory symptoms, and a casual observation may convince the healthcare provider that the patient is resting quietly when in fact the patient is developing respiratory distress* [italics in original].[47]

Finally, Dr. Becker concluded the following:[48]

> However, despite the sponsor's arguments, the Division remains concerned that the full extent and severity of pulmonary toxicity in the intended treatment population is unknown …
>
> Therefore, **it is likely that, even with adequate screening for pulmonary risk factors, some patients will require respiratory support post-dose, and some patients will be at risk for respiratory failure and death after administration of *Staccato* Loxapine** [emphasis added].

V. Psychopharmacologic Drugs Advisory Committee assessment

On December 12, 2011, PDAC considered the NDA for inhaled loxapine. On the overarching question of whether inhaled loxapine should be approved for use as a single dose in 24 hours when used with the FDA-proposed REMS as a treatment for agitation in patients with schizophrenia or bipolar I disorder, the committee members were nearly evenly divided with nine members voting yes, eight voting no, and one abstaining. Thus, nearly half of the members opposed approval, even if limited to a single dose in 24 hours and used under the FDA-proposed REMS.

VI. Summary and conclusions

In conclusion, we strongly oppose FDA approval of the NDA for inhaled loxapine for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults because (1) there is no evidence from clinical trials that inhaled loxapine offers any significant or unique benefits over currently available FDA-approved treatments for acute agitation in such patients; and (2) there is unequivocal evidence that the drug — even after a single dose — can cause significant life-threatening pulmonary toxicity. As the FDA's own analysis demonstrated, there is no reasonable justification for approving this drug, and doing so would recklessly endanger patients' lives. There is no reason to believe that carving out a restricted approval for inhaled loxapine by limiting exposure to a single dose under a REMS would be sufficient to prevent serious pulmonary toxicity from occurring and to protect public health.

Clearly, there is not substantial evidence that inhaled loxapine is safe. On the contrary, there is substantial evidence that the drug is unsafe and can cause life-threatening harm. This risk, combined with the lack of significant benefits in comparison to safer FDA-approved alternatives, leads to the conclusion that the only reasonable course of action is for the FDA to disapprove the NDA for inhaled loxapine. Allowing this drug to be marketed, even at a single dose and under a REMS, would result in a large number of preventable injuries and deaths.

Rather than issuing a complete response letter to the initial NDA submission for inhaled loxapine from Alexza Pharmaceuticals, the FDA should have issued a more definitive letter of disapproval. Such a letter should certainly be issued in response to the company's resubmitted NDA.

Thank you for considering our comments in this very important matter.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

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