# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022549Orig1s000**

# SUMMARY REVIEW

**M E M O R A N D U M** DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE**: 21 December 2012

**FROM**: Mitchell V. Mathis, M.D.
Acting Director
Division of Psychiatry Products, HFD-130

**TO:** File NDA 22549 [21 June 2012 resubmission]

**SUBJECT:** Approval recommendation for Staccato Loxapine for Inhalation for the treatment of agitation associated with schizophrenia and bipolar disorder

**Background and Regulatory History**

Loxapine is a typical antipsychotic first approved in 1975 for the treatment of schizophrenia. Staccato Loxapine for Inhalation is a single-use device that thermally generates loxapine aerosol when activated by the patient's inhalation. This new dosage form is intended to be used for the treatment of agitation associated with schizophrenia or bipolar disorder, an indication already approved for three immediate release intramuscular forms of atypical antipsychotics (Zyprexa, Geodon, and Abilify). This new dosage form offers several clinical advantages to the injectable drugs currently available (e.g., not painful, less invasive, but still with rapid onset of action).

The original application was submitted on 11 December 2009 and consisted of two placebo-controlled, fixed dose studies (5 mg and 10 mg), one in agitated patients with schizophrenia, and the other in agitated patients with bipolar disorder. The endpoint for the trials was change from baseline at 2 hours for the PANSS Excited Component (PEC), a measure of agitation. Both doses were highly statistically significant vs. placebo at 2 hours. Additionally, the time course of effect could be seen and the effect was observable at the first measurement at 10 minutes post-dose. The effect size was numerically larger for the 10 mg dose than it was for the 5 mg dose.

The primary safety concern was bronchospasm in studies specifically designed to look at respiratory safety in patients with asthma and COPD. FEV1 was the primary safety measure in these trials. Patients were allowed two 10 mg doses separated by 10 hours; the second dose at 10 hours could be given only if FEV1 did not decrease more than 20% after the first dose. These trials were placebo-controlled (placebo was the same inhaler without the drug). For the asthma study the mean change in FEV1 was a decrease of about 300 mL with the first dose and over 500 mL with the second dose. Respiratory symptoms requiring albuterol rescue were noted in 54% of drug patients and 12% of placebo patients. Nine of 26 drug-exposed patients (and 1 of 26 placebo-exposed patients) were ineligible to receive the second dose due to decrease in FEV1 (from the first dose) that precluded dosing again. For the COPD study, the mean change in FEV1 was a decrease of about 100 mL after dose one and about 125 mL after the second dose. Respiratory symptoms were noted in 19% of drug exposed patients vs. 11% of placebo patients; 23% of drug patients and 15% of placebo patients required albuterol rescue. Seven of 25 drug-exposed patients (and 1 of 27 placebo-exposed

patients) were ineligible to receive the second dose due to FEV1 drop of 20% or respiratory symptoms from the first dose. When patients with pulmonary disease were excluded from the clinical trials, there were very few respiratory adverse reactions (0/263 pbo, 2/265 5 mg, 2/259 10 mg).

The Division issued a Complete Response Letter on 8 October 2010 after concluding that while efficacy was clearly demonstrated, safety in patients with respiratory disease was a concern that would require a plan in place prior to approval to assure safe use. In addition, there were several manufacturing issues, including an inspection with several deficiencies.

The sponsor responded to the CR letter on 8 April 2011 and attempted to address our concerns about pulmonary safety. We took the application to the Psychiatric Drugs Advisory Committee (PDAC) Meeting. The PDAC was composed of 6 psychiatrists, 5 pulmonologists, one statistician, 4 Drug Safety and Risk Management (DSARM) members, one consumer representative and one patient representative. The vote was 17 yes to 1 no that the drug had been shown to be effective. There was a great deal of discussion about how doses subsequent to the first were more likely to cause clinically significant decreases in FEV1, and so the initial safety question to the committee, which included the sponsor's proposed multiple doses/24 hrs strategy, was voted down with 12 no votes to 5 yes votes, even with the FDA Risk Evaluation and Mitigation Strategy (REMS) in place. As a result of the obvious discomfort with subsequent doses, we asked the PDAC to vote on a single dose within 24 hours with the FDA REMS in place and the vote was 9 yes, 8 no, and 1 abstention.

The sponsor incorporated the FDA-proposed REMS into their 10 Jan 2010 submission including labeling that limits the dose to one per 24 hours. We extended the review clock to 5 May 2012 to allow time to evaluate this new information. The numerous manufacturing issues were not addressed in that submission and so a second CR Letter was issued to address these deficiencies.

The current submission (21 June 2012) now represents the third cycle of review for this NDA. This response includes new CMC information to address the identified manufacturing deficiencies and to finalize the labeling and the REMS. (b) (4)

**Substance of this CR Response**

Dr. David Claffey performed the CMC review. Many CMC issues had been resolved with the multiple cycles of review of this product. One outstanding issue was (b) (4) In his original review for this cycle, Dr. Claffey noted that an Office of Compliance recommendation was necessary prior to approval. On 20 December 2012, CDER-OC issued an overall recommendation of "acceptable" for the application and so Dr. Claffey amended his review to recommend approval.

**Revised REMS**
The sponsor agreed with FDA and the PDAC that this product must only be used in settings where pulmonary rescue (including advanced treatments of nebulization, intubation, and mechanical ventilation) can be performed if required. All patients must be screened for historical or physical exam evidence of pulmonary disease and must be monitored for respiratory symptoms and signs (including vital signs and chest auscultation) every 15 minutes for at least 1 hour after the single allowable dose per 24 hours.

The REMS includes healthcare facility certification and a communication plan. The REMS oversight committee found the plan acceptable.

**Revised Labeling**
We have negotiated a boxed warning for bronchospasm with prominent mention of the REMS. The dose is limited to one per 24 hours, (b) (4)

**Clinical**
Drs. Levin and Becker have recommend approval.

**Pulmonary**
Dr. Theresa Michele and her team concluded that the proposed labeling and REMS will mitigate the risk of pulmonary adverse reactions for this product.

**Observational Study**
We determined early on in the review of the pulmonary safety issues that a post-marketing examination of "real world" use would be informative about the safety of the product and how our REMS performs to protect patients. The sponsor agreed to look at 10,000 exposures after approval to assess the risk of using the product with the current labeling and REMS. The protocol for this study has been submitted and is currently under review by our clinicians and the Division of Epidemiology.

**Pediatric Plan**
The sponsor has submitted a pediatric development plan to study down to age (b) (4) for agitation in schizophrenia and 10 years for agitation in bipolar disorder. A partial waiver for younger children was requested. The PeRC granted these waivers. We will be discussing the pediatric development plan with PeRC when protocols are submitted.

**Conclusions and Recommendations**
Agitation in schizophrenia and bipolar patients is difficult to manage clinically and is distressing and dangerous to patients. This product offers an effective option to treat acute agitation in schizophrenic and bipolar patients, and adds a different option for the treating physician to choose from—prior to this device, the pharmacologic options to control agitation were oral dosage forms (slow and variable onset) and injectable medications (invasive/painful). No patients, including those patients in the special safety studies, experienced unmanageable adverse reactions; our REMS ensures proper selection and management of patients. I believe that the benefits outweigh the risks when the product is used according to the labeling and REMS we have developed. The sponsor has agreed to look at a large number of patients after approval to assess adverse reactions and to assess how well the REMS is performing to identify patients who should not receive the medication and to

keep those who are candidates safe with careful monitoring after each dose. The review team has recommended approval of this product and I agree with the team. The manufacturing issues have been resolved to the CMC team's satisfaction. Labeling has been negotiated and finalized.

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MITCHELL V Mathis
12/21/2012