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April 1, 2021

Tiffany Farchione, MD, FAPA, Director (Acting)
Division of Psychiatry Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

RE: NDA 022549 ADASUVE® (loxapine) Inhalation Powder
DEFERRAL EXTENSION REQUESTED
RESPONSE TO PREA NON-COMPLIANCE LETTER

Dear Dr. Farchione,

Reference is made to Alexza Pharmaceuticals, Inc. (Alexza) New Drug Application (NDA) 022549 for ADASUVE® (loxapine) Inhalation Powder (ADASUVE), approved on December 21, 2012 for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

The purpose of this letter is to respond to the FDA's Notification of PREA Non-Compliance letter dated February 19, 2021. As discussed below, Alexza is hereby requesting an extension of the deferral for Final Report Submission until January 31, 2024. Alexza believes that this time period is needed in order to conclude discussions with the Agency regarding the ongoing review of the ADASUVE REMS Modification, and allow sufficient time to assess the commercial viability of continued marketing of the product under the REMS Modification.

Background

The NDA approval letter for ADASUVE describes two deferred Post Marketing Requirements (PMRs) under PREA (PMR 1891-1 and 1891-2), with the following timelines:

1891-1 A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. A study to obtain pharmacokinetic data and provide information pertinent to dosing of Adasuve (loxapine) inhalation powder in the relevant population.

Final Protocol Submission Date: May 1, 2013

	Study/Trial Completion Date:	July 18, 2013
	Final Report Submission:	January 18, 2014 (deferral extension granted to August 31, 2015)

1891-2 A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. A study of the efficacy and safety of Adasuve (loxapine) inhalation powder in the relevant pediatric population.

Final Protocol Submission Date:	October 1, 2013
Study/Trial Completion Date:	September 30, 2014
Final Report Submission:	March 30, 2015

PMR 1891-1 has been completed, and a final report was timely submitted on August 31, 2015. With regard to PMR 1891-2, the Agency previously granted deferral extension requests in 2013 and 2018, to extend the Study/Trial Completion Date to July 31, 2020 and the Final Report Submission Date to January 31, 2021.[1]

Deferral Extension Requested for PMR 1891-2

Alexza confirms that study PMR 1891-2 has been delayed. Accordingly, this submission constitutes Alexza's Deferral Extension Request, requesting an extension of the Study/Trial Completion Due Date and Final Report Due Date for PMR 1891-2. The rationale for this request is presented below.

The ADASUVE NDA (NDA 022549) was approved with a REMS with ETASU to mitigate the potential risk of respiratory events. Since product launch, market uptake of ADASUVE has been low, in large part due to the burden imposed by the REMS, notwithstanding the positive safety profile demonstrated over more than seven years of post-marketing experience.

To address the company's concerns regarding the REMS, Alexza initiated discussions with the Division of Psychiatry nearly two years ago. Specifically, (b) (4) [redacted], Alexza and the Division have continued to work together to seek agreement on proposed changes to the ADASUVE REMS. To that end, Alexza

[1] We note that the online PMR database appears to have an incorrect date listed. The Original Projected Completion Date is identified as July 31, 2021.

and the Division met several times in 2020 (March 12, July 24, and November 6). The result of these interactions was the recent submission of a REMS Modification (January 13, 2021), which is currently under review by the Division. This nearly two-year effort to modify the REMS to reduce the burden to patients and providers has delayed the scheduled conduct and completion of PMR 1891-2.

Despite the low market uptake of ADASUVE and the burden to healthcare providers of the current REMS, Alexza continues to believe the product offers an important treatment option to patients and remains committed to continued marketing of the product if at all possible. That being said, Alexza is awaiting the Division's review of the pending REMS modification submission in order to assess the feasibility of continued marketing of the product and, consequently, of conducting PMR 1891-2. Completion of FDA review of the REMS Modification is anticipated mid-year 2021. The new proposed study completion date for PMR 1891-2 would allow for sufficient time to assess the impact of the REMS Modification on commercial viability of ADASUVE and to conduct the PMR study. As a result, the company therefore requests that the due dates for completion of PMR 1891-2 be extended for three years, as follows:

Study completion date: July 31, 2023

Final report submission: January 31, 2024

(Note that the final study protocol was submitted on September 25, 2018; IND 073248 Sequence 0110.)

Alexza remains committed to the development of pediatric labeling. We believe that the proposed extension will not create a safety risk to the pediatric population because, to the best of our knowledge, there has been no off-label use of ADASUVE in pediatric patients in the commercial setting.

Please feel free to contact me by email (ekamemoto@alexza.com) or phone (650-704-7301) if you have any questions regarding this submission or require additional information.

Sincerely,

Edwin S. Kamemoto
Regulatory Affairs & Drug Safety
Alexza Pharmaceuticals, Inc.

cc: Latrice Wilson

APPEARS THIS WAY ON ORIGINAL

Antivirus Statement

Number and Type of Electronic Media	Electronic transmission via ESG
Size of Submission	Approximately 3 MB
Virus Protection Statement	This submission is virus free.
Software Information	Sophos Endpoint

Technical Point of Contact

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