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POSTMARKETING COMMITMENT CORRESPONDENCE

June 18, 2021

Rigoberto Roca, M.D.
Director, Division of Anesthesiology,
Addiction Medicine, and Pain Medicine
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attn: Kimberly Compton, RPh, Sr. Regulatory Project Manager

Re: **NDA 209229 – LUCEMYRA (lofexidine)**
Sequence Number 0174
Response to PREA PMR Non-Compliance Letter for PMRs 3391-1 & 3391-3

Dear Dr. Roca:

Reference is made to the following:

- NDA 209,229 Approval Letter dated May 16, 2018
- PREA Non-Compliance letter for PMRs 3391-1 and 3391-3 dated April 19, 2021.
- Submission of the final study report for [redacted] (b) (4) on May 12, 2021 (e-sequence 0170)
- Submission of the final study report for [redacted] (b) (4) was submitted to NDA 209,229 on October 24, 2019 (e-sequence 0082)
- Postmarketing correspondence dated July 23, 2018 (e-sequence 0035)
- Sponsor's email correspondence dated October 24, 2018
- Postmarketing Correspondence dated January 27, 2021 (e-sequence 0159)

- Submission of the final protocol for study [redacted] (b) (4) to IND 47857 on July 31, 2019 (e-sequence 0024)

This correspondence is submitted in response to the Pediatric Research Equity Act (PREA) Non-Compliance Letter for Postmarketing Requirements (PMRs) 3391-1 and 3391-3 dated April 19, 2021 and serves to notify the Agency that submission of the final study report for [redacted] (b) (4) Toxicity Study in Juvenile Rats [redacted] (b) (4) submitted on May 12, 2021 is intended to complete PMR 3391-1 (bolded and underlined text) and fulfill PMR 3391-3 as specified in the NDA 209,229 Approval Letter dated May 16, 2018.

3391-1	Conduct a juvenile animal study in rats from PND 36 to PND 90 to support pediatric drug development in children aged 12 to 17 years. The study will evaluate the effect of the drug on growth and development, specifically, reproductive capacity, bone development, and the central nervous system histopathology and long-term functional effects (learning and memory, motor function. reflexes, **and an assessment of social interaction or other higher-cognitive functioning**).
3391-3:	Conduct a juvenile toxicology in rats to evaluate the impact of lofexidine on early neuronal development during peak synaptogenesis to support pediatric studies in neonates and children under the age of 3.

The primary study intended to fulfill PMR 3391-1 ([redacted] (b) (4)) completed by March 2019. The final report for [redacted] (b) (4) was submitted on October 24, 2019 in partial fulfillment of PMR 3391-1. As described further in the Nonclinical Information Amendment accompanying the [redacted] (b) (4) final study report, the requirement to perform an assessment of social interaction or other higher-cognitive functioning was met through [redacted] (b) (4) as the in-life CRO for the primary study ([redacted] (b) (4) did not have the necessary technical expertise. As a result, fulfillment of PMR 3391-1 in its entirety was delayed, as previously discussed with the Division in Postmarketing Correspondence dated July 23, 2018 and in an email correspondence dated October 24, 2018. However, fulfillment of the Final Report Submission milestone was further delayed as a result of technical issues encountered with the positive control cohort required to for PMR 3391-3 which ultimately delayed completion of neurohistological analysis and complete reporting for [redacted] (b) (4) as described further below and in Postmarketing Correspondence dated January 27, 2021.

The agreed upon date for Final Report Submission for PMR 3391-3 was March 2021. The final protocol for [redacted] (b) (4) the study intended to fulfill PMR 3391-3, was submitted to IND 47857 on July 31, 2019 and in-life for the main study was completed by 05/2020. However, submission of the final report intended to fulfill the milestone was delayed as a result of technical issues encountered with the positive control cohort required to fulfill this PMR. The positive control groups that failed the main portion of the study were ultimately completed under a separate protocol in 11/2020. The samples were sent to the neurohistopathology lab in 12/2020 for processing. Unfortunately, the neurohistopathology lab was required to close due to Covid-19, which delayed completion of sample processing, staining, and analysis by several weeks which delayed complete reporting for [redacted] (b) (4) Additional details regarding the study and the delays encountered are provided in Postmarketing Correspondence dated January 27, 2021 and in the Nonclinical Information Amendment accompanying the [redacted] (b) (4) final study report.

USWM requests that all information in this file be treated as confidential to the extent possible in accordance with 21 CFR 20.61 and that no information from this file may be provided to any unauthorized persons without our written consent.

If you have any questions regarding this submission, please feel free to contact me via phone or email.

Sincerely,

Adam Reuther
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Electronic Submission Technical Information

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Symantec Endpoint Protection
Program Version	14 (14.0 RU1 MP2) build 3929 (14.0.3929.1200)
Virus Definition Date	June 17, 2021

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