azurity pharmaceuticals

Committed to making a difference in patients' lives.

09 April 2021

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research
5901-B Ammendale Rd
Beltsville, MD 20705

Re: Katerzia (amlodipine) Oral Suspension
NDA 211340
DEFERRAL EXTENSION REQUEST
RESPONSE TO PREA NON-COMPLIANCE LETTER
SN 0028

Dear Dr. Stockbridge:

Reference is made to the Azurity Pharmaceuticals, Inc. (Azurity) New Drug Application (NDA) 211340 for Katerzia® (amlodipine) Oral Suspension, approved by the Agency on 08 July 2019 for several indications including treatment of hypertension in adults and children 6 years and older.[1]

The purpose of this letter is to respond to the FDA's Notification of Non-Compliance with PREA letter dated 25 February 2021. Azurity is hereby requesting an extension of the deferral for Final Nonclinical Report Submissions until February 2022, in order to meet the Post Marketing Requirements (PMR) 3640-1 commitment. As discuss below, Azurity must conduct the nonclinical juvenile toxicity studies to support the required pediatric studies. Due to ongoing discussions with the Agency on the study designs, study delays due to COVID-19, and a change in the study site, the conduct of the toxicology studies was delayed until April 2021. Therefore, due to the delay in completion of PMR 3640-1, Azurity is also requesting an extension of the deferral for Final Clinical Report Submission until May 2027 for the PMR 3640-2 commitment. During this time, Azurity would like to continue discussions with the agency regarding a feasible study design to satisfy the requirements of the company's PREA obligations with regard to Katerzia PMR 3640-2 commitment.

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[1] At the time of NDA approval, the Katerzia NDA was held by Silvergate Pharmaceuticals, Inc. (Silvergate). The NDA is now held by Azurity Pharmaceuticals, Inc. (Azurity), which was created in June 2019 following the acquisition of Silvergate by CutisPharma. Integration of the combined companies required evaluation of drug product portfolios and regulatory commitments.

The NDA approval for Katerzia described two deferred Post Marketing Requirements under PREA (PMR 3640-1 and 3640-2). The original timelines included in the NDA approval letter are provided below.

3640-1 Conduct non-clinical toxicity studies in juvenile rats to evaluate the developmental toxicity to include assessment of the effect of amlodipine benzoate suspension on reproductive and learning development to support dosing in humans down to birth

Final Protocol Submission:	07/2019
Study Completion:	07/2020
Final Report Submission:	01/2021

3640-2 Conduct a dose-ranging, safety, tolerability, and efficacy study with amlodipine benzoate oral suspension in hypertensive pediatric patients age birth to less than 6 years of age

Final Protocol Submission:	04/2021
Study Completion:	10/2025
Final Report Submission:	04/2026

On 26 April 2018, Azurity's predecessor-in-interest, Silvergate, received comments from the Agency related to the Initial Pediatric Study Plan (iPSP) for Katerzia. The Agency required that a juvenile rat toxicity study be completed prior to conducting a study in children less than 6 years of age.[2] Azurity has been interacting with the FDA on the development of juvenile toxicity (JT) Study 3640-1 from May 2018 to April 2020. During this time, Azurity furthered discussion with the Agency to identify an adequate study design to meet the JT PMR commitment. Protocol revisions were submitted to the Agency on 06 March and 13 April 2020, at which time the Agency confirmed agreement with the study design.[3-4]

Azurity initially awarded the rodent JT studies (PMR 3640-1) to the (b) (4) . The project was initiated and protocols from this location were drafted and submitted to the Agency.[3-4] However, due to the acquisition of (b) (4) segment, the study work was transferred to the (b) (4) (b) (4) location. This change in site location (b) (4), as well as the COVID-19 pandemic and associated workplace and travel restrictions, resulted in a significant overall delay of the program. The COVID-19 pandemic imposed numerous obstacles including the inability to perform a GLP audit and qualification of the (b) (4) facility until (b) (4) Due to the change in study location, (b) (4) required that the study protocols be reformatted into the standard format used at the (b) (4) site. In addition, minor changes were made to the study design to reflect current Test Facility (b) (4) procedures, as

[2] PIND 116485 Initial Pediatric Study Plan FDA Comments, (26 April 2018)
[3] PIND 116485 Response to Advice/Information Request, (06 March 2020)
[4] PIND 116485 Nonclinical Information Amendment, (13 April 2020)

outlined in a letter from (b) (4). For that reason, updated protocols were submitted to the Katerzia PIND 116485 on 18 March 2021.[5]

Deferral Extension Request

As a result of the delay in JT Study 3640-1, a deferral extension is being requested for both the JT Study 3640-1 and the Pediatric Study 3640-2. Completion of Study 3640-2 is dependent on completion of JT Study 3640-1 thus, both proposed timelines have been adjusted.

To fulfill the requirements of the JT PMR 3640-1 study commitment two studies will be conducted. Timelines for both JT studies and the pediatric study are provided below.

3640-1 Conduct non-clinical toxicity studies in juvenile rats to evaluate developmental toxicity to include assessment of the effects of amlodipine benzoate suspension on reproductive and learning development to support dosing in humans down to birth

(b) (4)

Final Draft* Protocol Submission:	03/2021
Study Completion:	09/2021
Final Report Submission:	01/2022

*Considered draft pending MTD results

(b) (4)

Final Draft* Protocol Submission:	03/2021
Study Completion:	12/2021
Final Report Submission:	02/2022

*Considered draft pending range-finding results

3640-2 Conduct a dose-ranging, safety, tolerability, and efficacy study with amlodipine benzoate oral suspension in hypertensive pediatric patients age birth to less than 6 years of age.*

Final Protocol Submission:	04/2022
Study Completion:	10/2026
Final Report Submission:	04/2027

(b) (4)

[5] PIND 116485 Information Amendment: Nonclinical, (18 March 2021)

Azurity respectfully requests that public posting of this Response Letter to the Notification of Non-Compliance with PREA be delayed until the request for deferral extension, in accordance with 505B(a)(3)(B)(i), has been evaluated by FDA.

Under no condition is the disclosure of any portion of the attached materials to any person or entity other than the Food and Drug Administration authorized without prior consent of the applicant.

This application has been prepared in electronic Common Technical Document (eCTD) format in accordance with FDA' s Guidance for Industry: Providing Regulatory Submissions in Electronic Format-Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. This submission has been transmitted via the Electronic Submissions Gateway. A description of the electronic submission is provided.

Additionally, we ask that all communications regarding this application be sent to Korie Osborn and me. Our contact information is provided.

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Sincerely,

Michael C. Beckloff