azurity pharmaceuticals

Committed to making a difference in patients' lives.

May 24, 2024

Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products
Food and Drug Administration
Center for Drug Evaluation and Research
via Electronic Submission Gateway

NDA 200796
Sequence 0121
Edarbi (azilsartan medoxomil) tablets, 40mg and 80 mg

Response to PREA Non-Compliance Letter
Deferral Extension Requested

Dear Dr. Stockbridge:

Reference is made to IND 71,867 and NDA 200796 for Edarbi (azilsartan medoxomil) tablets, 40 mg and 80 mg, approved on February 25, 2011 for the treatment of hypertension. Reference is also made to the Notification of Non-Compliance with PREA, dated April 9, 2024. Azurity Pharmaceuticals, Inc. (Azurity) submits this response to the Notification of Non-Compliance with PREA in accordance with the provisions of section 505B(d)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355c(d)(1)].

Reference is made to the original PMR (previously PMR 1733-3, currently PMR 1733-5) issued in the Approval letter for NDA 200796, stated as follows:

> *An efficacy and safety, dose-finding study in children 12 months and older, weighing less than 25 kg, with secondary hypertension.*
>
> *Final Protocol Submission:* *April 2016*
> *Study/Trial Completion:* *September 2020*
> *Final Report Submission:* *April 2021 (updated to December 2021)*

The original PMR 1733-3 was revised in the Release from Postmarketing Requirement and New Postmarketing Requirement letter dated December 22, 2021 to PMR 1733-5, stated as follows:

> *A safety and pharmacokinetic study to identify a dosing regimen for azilsartan medoxomil in pediatric patients 2 to <6 years of age with hypertension and weighing <25 kg.*
>
> *Final Protocol Submission:* *01/2022*
> *Study Completion:* *07/2023*
> *Final Report Submission:* *09/2023*

Reference is further made to the Type C Meeting held with the Agency on September 4, 2018 to discuss a protocol amendment for PMR 1733-4 in which the Agency requested that the sponsor assess and propose alternate study designs for meeting the Postmarketing Requirement in the 2 to <6 years of age population. The sponsor subsequently met with the Agency on October 1, 2020 and March 30, 2021 to discuss proposed alternate study designs. Agreement on a proposed study design was reached during the March 2021 meeting and a draft synopsis was submitted on April 30, 2021. Also, as a result of the March 2021 meeting, the final report submission due date for the original PMR 1733-3 was extended from April 2021 to December 2021 to allow for finalization of the proposed study design and submission of a request to be released from PMR 1733-3 with subsequent issuance of the new PMR 1733-5 according to the agreed upon study design. Azurity subsequently submitted an initial draft protocol on August 31, 2021 and a revised protocol on December 23, 2021 addressing comments received from the Agency on the draft synopsis and draft protocol, respectively.

During review of the initial draft protocol, the Agency provided an Information Request which included a request to confirm whether the formulation used in a prior relative bioavailability (rBA) study would be used in the proposed clinical study. Azurity provided confirmation along with the revised protocol on December 23, 2021. Based on the confirmation that the formulation would be the same as used in the prior rBA study, the Agency provided an Advice/Information Request letter on March 9, 2022 raising a safety concern regarding the use of one of the proposed excipients in the intended patient population. Based on this concern and lack of supporting data for use of the excipient in the intended study population, Azurity proposed to reformulate the age-appropriate formulation to remove the excipient and noted that the reformulation process was expected to take between 18 and 24 months. The Agency agreed that a reformulation was strongly recommended in an Advice/Information Request letter dated August 2, 2022. Azurity proposed a revised formulation in a Type C Meeting (Written Response Only) request dated July 3, 2023. The Agency confirmed there were no clinical safety concerns with the proposed reformulated age-appropriate formulation on September 15, 2023.

During the summer of 2021, Azurity began working with (b) (4) finalizing the study design with the FDA. Efforts to (b) (4) with the FDA agreed study requirements continued in parallel with the work to reformulate the age-appropriate formulation. The pediatric study requirements were finally (b) (4) with some revisions, in March 2024. The clinical study protocol for PMR 1733-5 was then revised to reflect (b) (4) and submitted to the Agency for review on April 10, 2024.

Since a [redacted] (b) (4) revised study protocol submitted to the FDA for review, Azurity is working to establish timelines for conduct of the PMR 1733-5 study. Azurity is working with the manufacturer of the age-appropriate formulation to produce the clinical trial material needed to supply PMR 1733-5 and anticipate availability of clinical trial material in early Q1 2025. Based on the timing for FDA approval of the revised protocol and production of the clinical trial material, the study is expected to be initiated by March 2025 and completed by February 2028. The resulting final clinical study report is expected to be finalized by September 2028.

Azurity acknowledges the importance of the PREA program and remains committed to fulfilling the post-marketing requirements under PREA and to completion of the studies requested by the Division as outlined in the Revised Written Request letter dated January 26, 2024. The need to reformulate the age-appropriate formulation directly resulted in delays to study initiation and therefore the submission of final study report. These circumstances were out of Azurity's control and could not have been reasonably anticipated at the time the original timetable for the new PMR 1733-5 was finalized.

Deferral Extension Request:

Due to the delays caused by the required reformulation of the age-appropriate formulation and [redacted] (b) (4) of the new FDA PMR 1733-5 study requirements [redacted] (b) (4) a deferral extension is being requested for the required PMR 1733-5 pediatric study. The proposed timelines are provided below.

Study Completion:	*02/2028*
Final Report Submission:	*09/2028*

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 conditions 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 submission is organized in accordance with the Agency's Guidance for Industry, "*Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using eCTD Specifications (February 2020)*." This submission has been transmitted via the Electronic Submissions Gateway. Attached, please find the electronic submission information.

Should you have any questions concerning this submission, please contact Justin Kilby at (470) 945-6284 or by e-mail at rasa@azurity.com. Alternately, you may contact Korie Osborn, Vice President Regulatory Affairs at rasa@azurity.com or (913) 389-7970.

Sincerely,

Korie Osborn
Digitally signed by Korie Osborn
Date: 2024.05.23 16:08:29 -05'00'

Korie Osborn on behalf of Justin Kilby
Vice President, Regulatory Affairs

This submission is being submitted in eCTD format. This electronic submission is approximately 2 MB in total size. All files were checked and verified to be free of viruses prior to being sent via the Electronic Submissions Gateway using CrowdStrike Antivirus Version 7.14.18408.0.