March 26, 2020

Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 200796 / Sequence 0090
Edarbi (azilsartan medoxomil) tablets, 40 mg and 80 mg

RESPONSE TO PREA NON-COMPLIANCE LETTER

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 February 10, 2020. Arbor Pharmaceuticals, LLC (Arbor) 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 1733-2, currently PMR 1733-4) issued in the Approval letter for NDA 200796, stated as follows:

> *An efficacy and safety, dose-finding study in children 6 years to less than 18 years with hypertension.*
>
> *Final Protocol Submission:* *March 2012*
> *Study/Trial Completion:* *June 2015*
> *Final Report Submission:* *January 2016*

The original PMR 1733-2 was revised in the Release from Postmarketing Requirement and New Postmarketing Requirement letter dated March 20, 2015 to PMR 1733-4, stated as follows:

> *Conduct a comparative single-dose pharmacokinetic and safety trial of azilsartan between infants, children, and adolescents with hypertension and healthy adults. Using data from the PK and safety trial, conduct an efficacy and safety, dose-finding trial in children 6 years to less than 18 years with hypertension.*

Reference is further made to the deferral extension requests submitted on October 28, 2015 and June 15, 2018 which were granted by FDA on December 11, 2015 and July 25, 2018, respectively, extending the final report submission deadline until December 2019. Reference is

also made to the Type C Meeting held with the Agency on September 4, 2018 to discuss the protocol amendment for PMR 1733-4.

Initiation of the PMR 1733-4 study was delayed as data from PMR 1733-1, which experienced delays due to slower than anticipated enrollment and difficulties enrolling subjects aged 12 months to <6 years, were necessary to aid in designing the study. Finalization of the study design was further delayed by negotiations of the divergent requirements of the study design with the FDA and EMA. Completion of the study was delayed due to slower than anticipated enrollment across all study countries with particular challenges in enrolling two of the study subgroups despite concerted efforts to enroll the study. After extensive attempts to improve subject recruitment rate globally, Arbor met with the Agency in a Type C Meeting held on September 4, 2018 to discuss proposed changes to the protocol enrollment criteria and sample size. After receiving agreement to the proposed protocol changes from the FDA at this meeting, Arbor's global marketing partner submitted the amended protocol to EMA for review and alignment of PDCO requirements. The amended protocol and modified PDCO requirements were formally adopted by EMA on December 14, 2018 and enrollment was subsequently closed. The last patient was enrolled in the study in November 2018 and completed the open label phase in November 2019.

The clinical study report was finalized by Arbor in November 2019 which included assessment of data from the double-blind and withdrawal phases of the study. The initial version of the final study report did not contain an assessment of the open label phase of the study since the last patient visit occurred in November 2019. The study report then required review by our global marketing partner in order to ensure the report aligned with global health authority requirements. This review resulted in additional revisions to the report. Finalization of the study report to include the required revisions and the complete analysis of the open label phase of the study is near completion. The final study report is proposed to be submitted to the IND by May 1, 2020.

(b) (4)

Arbor 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 May 15, 2014.

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 the eCTD Specifications (February 2020)." Attached, please find the electronic submission information.

Should you have any questions concerning this submission, I may be reached at justin.kilby@arborpharma.com or by phone at 470-235-2341. Alternately, you may contact Allison Lowry, Senior Director, Regulatory Affairs at allison.lowry@arborpharma.com or at 678-334-2428.

Sincerely,

Justin Kilby

Digitally signed by Justin Kilby
DN: cn=Justin Kilby, o=Arbor Pharmaceuticals, LLC, ou=Regulatory Affairs, email=justin.kilby@arborpharma.com, c=US
Date: 2020.03.25 18:37:08 -04'00'

Justin Kilby
Senior Manager, Regulatory Affairs

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