1 October 2021

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Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 202342, eCTD Sequence #0101
Product Name: Esomeprazole Strontium Delayed Release Capsules 24.65 mg and 49.3 mg
Subject: RESPONSE TO PREA NONCOMPLIANCE LETTER

Dear Dr. Lee:

Please refer to the New Drug Application (NDA 202342) for Esomeprazole Strontium Delayed Release Capsules held by Belcher Pharmatech, LLC, a wholly owned subsidiary of Belcher Pharmaceuticals, LLC ("Belcher"). Reference is also made to the following:

- FDA's 5 May 2021 Notification of Non-Compliance with PREA letter regarding the Postmarketing Requirements (PMRs) 2054-2 and 4
- Belcher's 18 June 2021 response to the 5 May 2021 Notification of Non-Compliance with PREA letter, which included a request for deferral of pediatric studies
- FDA's 4 August 2021 Deferral Extension Denied letter
- FDA's 4 August 2021 Notification of Non-Compliance with PREA letter regarding the PMRs 2054-1 and 3

This submission provides Belcher's response to the Notification of Non-Compliance with PREA letter of 4 August 2021. Regarding the earlier correspondence referenced above regarding the pediatric PMRs, the following are noted:

- The FDA sent two separate Notification of Non-Compliance with PREA letters, one for PMRs 2054-2 and 2054-4 (on 5 May 2021) and a second for PMRs 2054-1 and 2054-3 (on 4 August 2021).
- In Belcher's 18 June 2021 response to the initial Notification of Non-Compliance with PREA letter, Belcher addressed all four PMRs (2054-1, 2, 3, and 4) by providing the reasons for the delayed pediatric assessment and a date by which Belcher expected to submit the assessments
- Belcher's 18 June 2021 response also included a request for deferral extension for the required pediatric studies (PMRs 2054-1, 2, 3, and 4)
- The FDA denied the deferral extension on 4 August 2021

As noted above, Belcher's reasons for the delayed pediatric assessments for the PMRs 2054-1, 2, 3, and 4 were provided in the letter of 18 June 2021. For completeness, they are provided again in this letter. In addition, Belcher requested a deferral extension in the 18 June 2021 letter, with proposed final report submission dates as follows:

- 2054-1: December 2025
- 2054-2: December 2028
- 2054-3: June 2026
- 2054-4: December 2028

Since Belcher's request for a deferral extension was denied, Belcher will not be requesting another extension. However, at this time and based on the reasons provided for the delayed studies, Belcher does not consider it feasible to complete the studies on a faster timeline than that proposed in the deferral request. Belcher remains committed to completing the required studies in a timely manner and plans further correspondence to address all 4 PMRs. In particular, reference is made to the Deferral Extension Denied letter which stated that FDA's "thinking has changed regarding the assessment of NSAID-associated gastric ulcer and the eradication of Helicobacter pylori in pediatric patients since PREA PMRs 2054-3 and 2054-4 were issued." Belcher appreciates the FDA's comments in the letter and will plan further follow-up.

Reasons for the Delayed Pediatric Assessments (Previously Provided in Belcher's 18 June 2021 Response To PREA Noncompliance Letter)

On 23 February 2020, ownership of NDA 202342 was transferred to Belcher. Prior to this, the following key activities related to conduct of pediatric postmarketing studies occurred:

At the time of approval of NDA 202342 on 6 August 2013, the following 4 postmarketing studies were required, with final report submission expected as indicated:

- 2054-1: Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for healing and maintenance of healing of erosive esophagitis (EE) in patients 1 month to 17 years, inclusive. The study must also assess the efficacy of esomeprazole strontium in maintenance of healing of EE, including determination of the dose and treatment duration required to maintain healing of EE in this pediatric population. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on bone, given that pediatric patients undergo different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.
    - Original Required Final Report Submission Date: April 2018

- 2054-2: Deferred pediatric study under PREA to evaluate the safety of esomeprazole strontium for treating symptomatic gastroesophageal reflux disease (GERD) in patients 1

year to 17 years, inclusive. The study must include an adequate number of patients in different pediatric age groups to evaluate the effect of esomeprazole strontium on bone, given that pediatric patients undergo different rates of growth depending on age. Baseline and posttreatment bone-related safety assessments must be included. This study may not be needed if the data from PMR 2054-1 are adequate to fulfill the requirement.
    - Original Required Final Report Submission Date: April 2021

- 2054-3: Deferred pediatric study under PREA to evaluate the pharmacokinetics, pharmacodynamics, and safety of esomeprazole strontium for reducing the risk of NSAID-associated gastric ulcer in patients 2 years to 17 years, inclusive. The study must include an adequate number of patients in different age groups to inform dosing, and to evaluate the effect of esomeprazole strontium on bone, given that pediatric patients undergo different rates of growth depending on age. Baseline and post-treatment bone-related safety assessments must be included.
    - Original Required Final Report Submission Date: October 2018

- 2054-4: Deferred pediatric study under PREA to evaluate the safety and efficacy of esomeprazole strontium in combination with clarithromycin and amoxicillin for the eradication of Helicobacter pylori in symptomatic pediatric patients 2 to 17 years, inclusive, with or without duodenal ulcer disease.
    - Original Required Final Report Submission Date: April 2021

Following an earlier transfer of NDA ownership, the previous owner of the NDA submitted a request on 27 March 2017 (sequence 0072) to defer the conduct of the required postmarketing pediatric studies. In response, the FDA requested a proposal for the timing of study protocol submission and study completion. Accordingly, in a 14 May 2018 submission (sequence 0080), the NDA owner proposed timing for these activities. The FDA then denied the deferral extension on 16 May 2019. The previous owner subsequently decided to divest of the product and discontinue marketing, and on 26 June 2019 (sequence 0089) submitted a request to withdraw NDA 202342 effective 30 September 2019.

In the NDA Annual Report submitted on 26 September 2019 (sequence 0090), the NDA holder confirmed that they had no plans to complete the pediatric studies since they had requested withdrawal of the NDA and had discontinued marketing the product. Esomeprazole Strontium Delayed Release Capsules have not been marketed since before the effective NDA withdrawal date, and the application is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) as discontinued.

Ownership of NDA 202342 was transferred to Belcher on 23 February 2020. Before this time, no progress was made on the conduct of the pediatric postmarketing studies, including protocol development, nor did any development of pediatric dosage forms that will be needed to conduct the studies take place. Since acquiring ownership of NDA 202342, Belcher has been transferring the manufacturing of Esomeprazole Strontium Delayed Release Capsules and intends to proceed

with pediatric formulation and protocol development followed by conduct of the required pediatric postmarketing studies.

As mentioned in earlier correspondence, Belcher regrets the delay in the conduct of the required pediatric studies and recognizes the importance of pediatric evaluations in drug development. If there are any questions please do not hesitate to contact me by phone 727-471-0850 Ext:250 or email me at mihirt@belcherpharma.com.

This submission is provided entirely in eCTD format; therefore, no Table of Contents is being provided. All electronic files included as the archival copy of this submission are provided via the FDA's electronic gateway. All files were checked and verified to be free of viruses using Symantec Endpoint Protection Version 14 (14.3) build 558 (14.3.558.0000).

Sincerely,

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