



NDA 203284/S-10

SUPPLEMENT APPROVAL

Horizon Therapeutics, LLC
Attention: Susan Telliard, MBA, MS
Senior Director Regulatory Affairs
150 S. Saunders Road
Lake Forest, IL 60045

Dear Ms. Telliard,

Please refer to your Supplemental New Drug Application (sNDA) dated February 27, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RAVICTI (glycerol phenylbutyrate) oral liquid, 1.1 grams/ml.

This Prior Approval Supplemental new drug application proposed to expand the approved indication to include patients less than 2 months of age. The indication is for the use of RAVICTI (glycerol phenylbutyrate) oral liquid, 1.1 grams/ml, as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (Prescribing Information, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since RAVICTI (glycerol phenylbutyrate) was approved on February 1, 2013, we have become aware of a signal suggesting an increased risk of serious neurological adverse reactions in patients with UCDs treated with RAVICTI who have elevated phenylacetic acid (PAA) blood concentrations. This signal is based on a published study of the use of Ravicti in healthy adults and in patients with hepatic impairment, in which a dose-dependent increase in the incidence of neurological adverse events was noted in those who received RAVICTI and who had elevated PAA blood concentrations. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of the serious risk of neurological adverse events associated with elevated PAA concentration in patients with urea cycle disorders.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to:

- 3527-1 Conduct analyses of clinical data (from clinical trials of Ravicti, patient registry(ies), or other sources) to evaluate associations between elevations in plasma PAA concentration (above pre-defined thresholds) and plasma PAA to PAGN ratio (above pre-defined thresholds) with: (a) the development of serious neurological adverse reactions, and (b) the risk of hyperammonemia in patients with urea cycle disorders (UCDs; both treatment-naïve and non-treatment-naïve) treated with glycerol phenylbutyrate (Ravicti). Associations should be assessed in UCD patients of all ages and compared to potential associations observed in healthy adults and in patients with non-UCD diagnoses treated with Ravicti. Correlate these data with potential dosage adjustment strategies of Ravicti in treatment-naïve and non-treatment-naïve UCD patients of different ages/age groups and in the context of: (a) normal plasma ammonia, and (b) elevated plasma ammonia (over a pre-specified threshold).

The timetable you submitted on November 14, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2019
Final Protocol Submission: 09/2019
Final Report Submission: 03/2020

Submit the protocol(s) to your IND 073480, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated February 27, 2018, containing the final report for the following postmarketing requirement listed in the February 1, 2013, letter.

2013-1: A clinical trial to assess the safety, efficacy, and PK of RAVICTI (glycerol phenylbutyrate) and its metabolites (PBA, PAA and PAGN) during RAVICTI (glycerol phenylbutyrate) treatment in pediatric patients with Urea Cycle Disorders who are under 2 months of age.

We have reviewed your submission and conclude that the above requirement was fulfilled.

Additionally, we remind you of your post-marketing requirement (PMR) 2013-4 listed in your February 2, 2013, approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jenny Doan, Regulatory Project Manager, at 301-796-1023.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Associate Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Prescribing Information
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA M SOULE
12/21/2018