



NDA 203284/S-005

**SUPPLEMENT APPROVAL/  
FULFILLMENT OF POSTMARKETING  
REQUIREMENT**

Horizon Therapeutics, LLC  
Attention: Jeffrey W. Sherman, M.D.  
Chief Medical Officer and Executive Vice President  
150 S. Saunders Road  
Lake Forrest, IL 60045

Dear Dr. Sherman:

Please refer to your Supplemental New Drug Application (sNDA) dated and received, June 28, 2016, received June 28, 2016, and your amendments, 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 provides for the use of RAVICTI (glycerol phenylbutyrate) oral liquid, 1.1 grams/ml, for use as a nitrogen-binding agent for chronic management of pediatric patients  $\geq 2$  months and  $< 2$  years of age with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. 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 text for the package insert and 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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 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 the potential for a reduced drug dosage delivery due to adherence of RAVICTI (glycerol phenylbutyrate) to nasogastric or gastric tubes when delivered in volumes of less than 1 milliliter. The results of your *in vitro* testing suggest drug loss when Ravicti (glycerol phenylbutyrate) is administered via gastric tube at volumes of 0.5 ml (70% drug recovery). Given the lack of information for doses between 0.5 ml and 1.0 ml, there is a potential serious risk of hyperammonemia in infants who receive volumes <1ml when administered via gastric or nasogastric tube. 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 identify this unexpected serious risk.

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 conduct the following study:

3214-1 *In vitro* study to assess the amount of Ravicti (glycerol phenylbutyrate) delivered through nasogastric and gastric tubes for dosing volumes less than 1 mL.

The timetable you submitted on April 20, 2017, states that you will conduct this study according to the following schedule:

Study Completion:	07/17
Final Report Submission:	08/17

Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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 action.

### **FULFILLMENT OF POSTMARKETING REQUIREMENT**

We have received your submission dated June 28, 2016, containing the final report for the following postmarketing requirement listed in the February 1, 2013, letter.

2013-2: A clinical trial to assess the safety, efficacy, and pharmacokinetics 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 2 months to <2 years of age.

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

Additionally, we remind you of your post-marketing requirements (PMRs) 2013-1 and 2013-4 listed in your February 2, 2013, approval letter that are 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 package insert(s) 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 package insert(s), 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, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, MD  
Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Label

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