CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203284Orig1s000

Trade Name: RAVICTI Oral Liquid, 1.1 grams/ml.

Generic Name: glycerol phenylbutyrate

Sponsor: Hyperion Therapeutics Inc.

Approval Date: February 1, 2013

Indications: This new drug application provides for the use of RAVICTI (glycerol phenylbutyrate) Oral Liquid, 1.1 grams/ml, for use as a nitrogen-binding adjunctive therapy for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) that 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 (eg, essential amino acids, arginine, citrulline, protein-free calorie supplements).

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203284

NDA APPROVAL

Hyperion Therapeutics Inc.
601 Gateway Boulevard
Suite 200
South San Francisco, CA 94080

Attention: Klara Dickinson
Sr. VP Regulatory Affairs

Dear Ms. Dickinson:

Please refer to your New Drug Application (NDA) dated December 23, 2011, received December 23, 2011, 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.

We acknowledge receipt of your amendments dated February 22, 2012; March 13, 23, and 27, 2012; April 20, 2012; June 29, 2012; July 3 and 5, 2012; August 23, 2012; December 7, 13, 28, and 31, 2012; January 1, 8, and 23, 2013.

This new drug application provides for the use of RAVICTI (glycerol phenylbutyrate) Oral Liquid, 1.1 grams/ml, for use as a nitrogen-binding adjunctive therapy for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) that 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 (eg, essential amino acids, arginine, citrulline, protein-free calorie supplements).

We have completed our review of this 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). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

We acknowledge your December 31, 2012, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Ravicti (glycerol phenylbutyrate) was not referred to an FDA advisory committee because this drug is not first in class; the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class; outside expertise was not necessary and there were no controversial issues that would benefit from advisory committee discussion.

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.

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 a signal of a serious risk of neurologic toxicity related to the use of Ravicti (glycerol phenylbutyrate) in pediatric patients

and in treatment-naïve patients, and as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate), and to assess a signal of a serious risk of carcinogenicity as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate).

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 these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of neurologic toxicity related to the use of Ravicti (glycerol phenylbutyrate) in pediatric patients and in treatment-naïve patients, and as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate), and to assess a signal of a serious risk of carcinogenicity as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate).

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

2013-1 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 under 2 months of age.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	August 2013
Trial Completion:	August 2017
Final Report Submission:	March 2018

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 ages 2 months to less than 2 years.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	July 2013
Trial Completion:	July 2016
Final Report Submission:	December 2016

2013-3 A milk-only lactation trial in lactating female patients with Urea Cycle Disorders receiving Ravicti (glycerol phenylbutyrate) to assess the pharmacokinetics of

Ravicti (glycerol phenylbutyrate) and its active metabolites in breast milk using an assay that has been validated in milk.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2013
Trial Completion:	June 2015
Final Report Submission:	December 2015

2013-4 A randomized, controlled clinical trial to assess the safety and efficacy of Ravicti (glycerol phenylbutyrate) in patients with Urea Cycle Disorders who are treatment naïve to phenylbutyrate.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	August 2013
Trial Completion:	June 2016
Final Report Submission:	March 2017

Submit the protocol(s) to your IND 073480, with a cross-reference letter to this NDA. Submit 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.

POSTMARKETING COMMITMENT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2013-5 To conduct an *in vivo* drug interaction study to evaluate the effect of Ravicti (glycerol phenylbutyrate) on the pharmacokinetics of a drug that is a sensitive substrate of CYP3A4/5 (e.g., midazolam).

The timetable you submitted on January 5, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2013
Study Completion:	March 2014
Final Report Submission:	July 2014

Submit clinical protocols to your IND 073480 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated December 23, 2011, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Ravicti (glycerol phenylbutyrate) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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 Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

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

Enclosure(s):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
02/01/2013