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*APPLICATION NUMBER:*

**203284Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA #                      NDA203284  
Product Name:                      Ravicti

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PMR/PMC Description:      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.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>December 2013</u>
	Study/Trial Completion:	<u>June 2015</u>
	Final Report Submission:	<u>December 2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A rat carcinogenicity study showed an increased incidence of malignancies. **In addition,** phenylacetic acid (PAA), the main metabolite of Ravicti, has been shown to cause neurotoxicity in clinical studies where it was given IV to cancer patients. A pre-approval study in lactating women was not possible due to the rarity (low prevalence) of Urea Cycle Disorders and the scarcity of lactating patients. However Ravicti is expected to be used by women of reproductive age and data on exposure of the drug via breast milk is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Because a rat carcinogenicity study showed an increased incidence of malignancies and because PAA has been shown to be neurotoxic, it is important to assess the presence of drug in breast milk. Milk only studies can provide information regarding timing of maternal dose relative to breast-feeding, the duration recommended to discard milk relative to maternal dose, and when to resume breast-feeding relative to maternal dose or drug exposure.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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5. Is the PMR/PMC clear, feasible, and appropriate?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
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NANCY C SNOW  
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01/31/2013



2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to gain data on the safety, efficacy and dosing in pediatric patients between the age of 2 months and 2 years in order to dose patients in this age group properly. Dosing for this age group for trials conducted under the NDA was not explored since all patients were converted from one medication, to Ravicti. The numbers of patients in this age group was too small to draw any meaningful conclusions. In addition PK data of the active drug/active metabolite were not regularly monitored in association with adverse events. Therefore the trials submitted with the NDA did not rule out a safety risk associated with the active metabolite.

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The ability of treatment naïve patients to tolerate Ravicti is an important safety issue. To ensure safe dosing of Ravicti when starting patients de novo, it is important to study an initial dosing and maintenance dosing algorithm based on protein intake, underlying disorder and catabolic/anabolic state in a controlled trial.

3. If the study/clinical trial is a PMR, check the applicable regulation.

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(b) (4)

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## PMR/PMC Development Template

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NDA/BLA # 203-284  
Product Name: Ravicti

PMR/PMC Description: 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).

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PMR/PMC Schedule Milestones: Final Protocol Submission: September 2013  
Study/Trial Completion: March 2014  
Final Report Submission: July 2014  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
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**In vitro studies suggested that phenylbutyrate, a metabolite of Ravicti, can potentially inhibit the metabolism of concomitant medications that are substrates of CYP3A4/5, CYP2D6 and/or CYP2C19. Since chronic administration of Ravicti is expected for UCD patients and the available alternative i.e. Buphenyl® also contains phenylbutyrate, the evaluation of the potential in vivo drug interaction with concomitant medications is warranted.**

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

**In vitro studies suggested drug interaction potential with substrates of three CYP enzymes, we are requesting one in vivo study with a substrate of CYP3A to adequately communicate the drug interaction potential to the prescribers by improving the labeling for drug interactions. The results of the study in combination of in vitro studies may be used to**

(b) (6)

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INSOOK KIM  
01/30/2013

EDWARD D BASHAW  
01/30/2013



The goal of the clinical trial is to establish PK/PD of the Ravicti metabolites, dosing algorithm, safety and efficacy in patients with UCDs under 2 months of age where there is theoretical concern of an inability to absorb the drug because of absence of fully developed pancreatic exocrine function with the subsequent loss of ammonia control.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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NANCY C SNOW  
01/30/2013

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01/30/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**Date:** January 29, 2013

**From:** Alyson Karesh, MD, Medical Officer  
Pediatric and Maternal Health Staff, Office of New Drugs

**Through:** Hari Cheryl Sachs, MD, Pediatric Team Leader,  
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, MD, Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** The Division of Gastroenterology and Inborn Errors of  
Metabolism, Office of New Drugs

**NDA:** 203284

**Sponsor:** Hyperion Therapeutics

**Drug:** glycerol phenylbutyrate, HPN-100 (Ravicti)

**Proposed Indication:** Adjunctive therapy for chronic management of adult and pediatric patients [REDACTED] (b) (4)

**Consult Request:** The Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP) consulted the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) for input on whether this product can ethically and feasibly be studied in patients less than 2 months of age, and for input on a PMR in children <6 years of age. See Appendix I for the full consult request.<sup>1</sup>

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<sup>1</sup> NDA 203284, Glycerol phenylbutyrate, HPN-100, Pediatric and Maternal Health Staff Request for Consultation, December 7, 2012.

**Background:** Briefly, the sponsor is seeking approval of Ravicti (glycerol phenylbutyrate) to treat UCD. Ravicti is a prodrug of phenylbutyrate and a pre-prodrug of phenylacetate, the active moiety.<sup>2</sup> The Ravicti submission includes two open label Buphenyl (sodium phenylbutyrate) to Ravicti switchover studies with data on 22 patients 2 months to 17 years of age. Both Ravicti and Buphenyl have the same active moiety.<sup>2</sup>

Buphenyl is approved<sup>3</sup>:

- as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)
- in all patients with neonatal-onset deficiency
- in patients with late-onset disease who have a history of hyperammonemic encephalopathy

Ravicti requires pancreatic enzymes, which may not be present until approximately 2 months of age, to cleave the glycerol from the drug product and convert it into its active form (phenylbutyrate). Therefore, Ravicti may not be effective in children less than approximately 2 months of age. DGIEP would like the sponsor to study pediatric patients less than 2 months of age, but in the meantime, because there is an approved alternative (Buphenyl), DGIEP is considering a contraindication for Ravicti in the <2 months of age population. DGIEP has also requested a Pediatric Ethics consult. See Appendix I for additional details.

**Pediatric PMHS Response to this Consult:** The Pediatric Team of the PMHS participated in multiple meetings between December 2012 and January 2013 with DGIEP and the Pediatric Ethics Team discussing the pediatric review issues for Ravicti application.

PMHS believes contraindicating Ravicti in patients less than 2 months of age is reasonable since there is no data to assess the efficacy of Ravicti in this population and there is an approved alternative. Labeling should specify why Ravicti is contraindicated in patients less than 2 months of age. Additionally, PMHS believes creating a post-marketing study requirement for this less than 2 months of age population is reasonable since Ravicti may have a lower powder burden and be more palatable than Buphenyl.<sup>4</sup>

Because of insufficient data in all patients less than 2 years of age, PMHS agrees with DGIEP that Ravicti should be approved only for patients 2 years of age and older. Additional safety, efficacy and dosing data will need to be collected to support use in patients less than 2 years of age.

PMHS has expressed a willingness to provide further input as requested.

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<sup>2</sup> NODA 203284, Glycerol phenylbutyrate (Ravicti), Clinical Review, review completion date November 27, 2012, final sign-off in Dartrts December 6, 2012.

<sup>3</sup> NDA 020572, Sodium phenylbutyrate (Buphenyl), March 31, 2009 labeling, accessed from Drugs@FDA, January 25, 2013.

<sup>4</sup> NDA 203284, Ravicti for Urea Cycle Disorders in Infants, Pediatric Ethics Memorandum, January 11, 2013.

**Appendix I:**  
Request for Pediatric and Maternal Health Staff Consultation<sup>5</sup>

1. Please briefly describe the submission including drug's indication(s):

“Ravicti is being developed for the chronic management of Urea Cycle disorders. The application contained one pivotal trial in patients over 18 years of age in which Ravicti was non-inferior to the approved drug Buphenyl. Both drugs are broken down into the same active metabolite, but Buphenyl is a salt, and Ravicti is a triglyceride with a glycerol backbone (see below). After the NDA was submitted the sponsor submitted a 15 patient pediatric study (age 29 days to <6 years) in which patients were crossed over from Buphenyl to Ravicti. All patients entered the trial already on Ravicti, and on day two were switched to Ravicti. PK and ammonia levels were checked at steady state for both drugs. The sponsor revised the proposed indication to include adult and pediatric patients. They also state in the label that [REDACTED] (b) (6) [REDACTED]”

2. Describe the reason for your consult. Include specific questions:

“Glycerol phenylbutyrate (Ravicti) is a nitrogen scavenging drug being reviewed for chronic management of Urea Cycle Disorders. It is a triglyceride attached to a glycerol backbone. The glycerol is hydrolyzed by pancreatic enzymes in the intestine, typically not present in neonates until about age 2-3 months. The development of pancreatic lipase is variable, and other forms of lipase are present at birth. A second nitrogen scavenging drug is already on the market, Buphenyl (NaPBA). For a neonate who presents within the first few hours or days of life with hyperammonemia the treatment is typically IV Ammonal and/or hemodialysis. Once stable patients are switched from Ammonal to Buphenyl (while still in the hospital), or if approved Ravicti. Because Ravicti requires pancreatic lipase to convert to its active form, we are concerned that patients in the first few months of life will be unable to metabolize the drug and will be at risk of hyperammonemia. Once broken down Ravicti and Buphenyl share the same active moiety, phenylacetic acid (PAA). The sponsor has already committed to a study “to assess safety, PK and ammonia control during Ravicti treatment in pediatric UCD patients under 2 months of age.” One of the objectives of the study would be to see whether Ravicti can be converted to its active form in these young patients in whom pancreatic lipase might not be fully developed. If they are unable to metabolize Ravicti their ammonia levels would increase, but because they would be in a monitored setting alternative treatments could be instituted right away. We request the input from PMHS regarding the feasibility and ethics of doing such a study.

We also request PMHS input regarding a PMR in children <6 years. In addition to safety and ammonia control this study would collect PK data on the active metabolite PAA. PAA has been associated with neurological adverse events at concentrations over 500mcg/mL. In this NDA AEs were not seen in association with elevated. However PAA levels were not consistently obtained and the number of patients

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<sup>5</sup> NDA 203284, Glycerol phenylbutyrate, HPN-100, Pediatric and Maternal Health Staff Request for Consultation, December 7, 2012.

(particularly in the youngest age group) was small. Dosing in the studies for the NDA was based on the dose of Buphenyl patients were on at the start of the study.'

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/s/  
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ALYSON R KARESH  
01/29/2013

HARI C SACHS  
01/29/2013

LYNNE P YAO  
01/30/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** January 29, 2013

**To:** Jessica Benjamin, Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Kendra Jones, Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP)  
Office of Prescription Drug Promotion

**CC:** Kathleen Klemm, Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP), OPDP

**Subject:** NDA 203284 - OPDP labeling comments for RAVICTI (glycerol phenylbutyrate) oral liquid

---

OPDP has reviewed the proposed draft Medication Guide for RAVICTI (glycerol phenylbutyrate) oral liquid submitted for consult on February 9, 2012, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled, "CLEAN proposed labeling.doc" sent via email from Jessica Benjamin on January 24, 2013, and were previously provided on January 28, 2013. OPDP's comments on the Medication Guide are based on the version sent from Latonia Ford (DMPP) on January 29, 2013.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding the proposed draft Medication Guide, please contact Kendra Jones at 301-796-3917 or [Kendra.Jones@fda.hhs.gov](mailto:Kendra.Jones@fda.hhs.gov).

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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KENDRA Y JONES  
01/29/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: January 28, 2013

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Errors  
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Raviciti (glycerol phenylbutyrate)

Dosage Form and Route: Oral liquid

Application Type/Number: NDA 203284

Applicant: Hyperion Therapeutics Inc.

## 1 INTRODUCTION

On December 23, 2011, Hyperion Therapeutics Inc. submitted for the Agency's review a 505(b)(1) New Drug Application (NDA) 203284 for Raviciti (glycerol phenylbutyrate) oral liquid. The Applicant's proposed indication is for use as a nitrogen binding adjunctive therapy in conjunction with dietary protein restriction for chronic management of adult and pediatric patients ( $\geq 2$  years old) with urea cycle disorders (UCDs).

On January 9, 2012, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Raviciti (glycerol phenylbutyrate) oral liquid.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) for Raviciti (glycerol phenylbutyrate) oral liquid.

## 2 MATERIAL REVIEWED

- Draft Raviciti (glycerol phenylbutyrate) oral liquid Medication Guide (MG) received on December 23, 2011, and received by DMPP on January 24, 2013.
- Draft Raviciti (glycerol phenylbutyrate) oral liquid Prescribing Information (PI) received on December 23, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on January 24, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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LATONIA M FORD  
01/28/2013

BARBARA A FULLER  
01/28/2013

LASHAWN M GRIFFITHS  
01/28/2013

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	RAVICTI™ (glycerol phenylbutyrate) oral liquid
Applicant	Hyperion Therapeutics, Inc.
Application/Supplement Number	NDA 203284
Type of Application	Original Submission
Indication(s)	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 (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements)
Established Pharmacologic Class <sup>1</sup>	None listed in HL
Office/Division	ODE III/DGIEP
Division Project Manager	Jessica Benjamin
Date FDA Received Application	December 23, 2011
Goal Date	January 23, 2013
Date PI Received by SEALD	January 28, 2013
SEALD Review Date	January 28, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

## Selected Requirements of Prescribing Information

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** .

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *There is no white space between each major heading in HL.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*

## Selected Requirements of Prescribing Information

• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

**NO**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

**Comment:** *The HL limitation statement is not bolded and must be bolded. There must be white space between this statement and the product title.*

#### Product Title

**NO**

10. Product title in HL must be **bolded**.

**Comment:** *Product title is not bolded and must be bolded.*

#### Initial U.S. Approval

**NO**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** *This is not an NME; therefore the Initial U.S. approval date in HL should not be "2013." It's the same active moiety as sodium phenylbutyrate. According to the Orange Book, the date is 1996. Ensure that correct initial U.S. approval date is entered in HL.*

#### Boxed Warning

**N/A**

12. All text must be **bolded**.

**Comment:**

**N/A**

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

**Comment:**

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

**Comment:**

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

**Comment:**

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

**Comment:**

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *There is not an established pharmacologic class(PC) listed in HL; however, in the DESCRIPTION section of the FPI, "nitrogen-binding agent" is listed. Must include PC in HL.*

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

**Comment:**

### Contraindications

## Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Must delete “. . . (b) (6)” from this statement. An email address, fax number, or general link to a company’s website does not meet the requirement to have adverse reaction reporting contact information in HL. It would not provide a structured format for reporting adverse reactions.

### Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: Since there is a Medication Guide for this drug product, must read: “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide” not “See 17 for PATIENT COUNSELING INFORMATION.”

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

## Selected Requirements of Prescribing Information

**Comment:** Subsections 14.1 and 14.2 in TOC must have lower case "w" for "with" and not read "With" so they exactly match subsection headings in FPI.

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

**Comment:**

- NO** 33. All subsection headings must be indented, not bolded, and in title case.

**Comment:** Subsection heading 2.2 (in the TOC and FPI) the word "From" should be sentence case and read "from."

- YES** 34. When a section or subsection is omitted, the numbering does not change.

**Comment:**

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS**" must be followed by an asterisk and the following statement must appear at the end of TOC: "\*Sections or subsections omitted from the Full Prescribing Information are not listed."

**Comment:** The statement at the end of the TOC should not be bolded. Unbold.

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION**".

**Comment:** This heading appears in smaller font size than the other headings in the FPI. Correct to be the same font size.

- YES** 37. All section and subsection headings and numbers must be **bolded**.

**Comment:**

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>

## Selected Requirements of Prescribing Information

8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:*** There are to be no periods after the section and subsection headings in the FPI. Delete the periods after each section/subsection heading in the FPI and the Table of Contents.

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

***Comment:*** There is a Medication Guide (MG) for this drug product. The MG does not appear at the end of the PI, and must upon approval.

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

***Comment:***

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

***Comment:***

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

***Comment:***

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

## Selected Requirements of Prescribing Information

### Comment:

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

### Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

### Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Comment:

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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/s/  
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JEANNE M DELASKO  
01/28/2013

LAURIE B BURKE  
01/28/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** January 28, 2013

**To:** Jessica Benjamin, Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kendra Jones, Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP), OPDP

**Subject:** NDA 203284 - OPDP labeling comments for RAVICTI (glycerol phenylbutyrate) oral liquid

---

OPDP has reviewed the proposed Prescribing Information (PI) for RAVICTI (glycerol phenylbutyrate) oral liquid submitted for consult on February 9, 2012, and offers the following comments. OPDP's comments on the proposed Medication Guide will follow under separate cover.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled, "CLEAN proposed labeling.doc" sent via email from Jessica Benjamin on January 24, 2013.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions, please contact Katie Klemm at 301-796-3946 or [Kathleen.Klemm@fda.hhs.gov](mailto:Kathleen.Klemm@fda.hhs.gov).

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KATHLEEN KLEMM  
01/28/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203284	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Ravicti Established/Proper Name: glycerol phenylbutyrate Dosage Form: liquid for oral administration Strengths:		
Applicant: Hyperion Therapeutics		
Date of Receipt: 12/23/11		
PDUFA Goal Date: 1/23/13		Action Goal Date (if different): 1/31/13
Proposed Indication(s): 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 $\geq 2$ 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).		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	2.1 Dosage and Administration 2.5 Nutritional Management 2.1 Dosage and Administration 5.6 Toxicity of Phenylacetate

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Literature sources were used to inform the label on the following:

- The usage of phenylacetate levels and urinary phenylacetylglutamine for informing initial dosage and adjustments
- The toxicity of phenylacetate
- The importance of nutritional therapy including protein restriction and amino acid supplementation in the management of patients with urea cycle disorders
- The rationale for contraindication in children under two months

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO”, proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).  
Buphenyl*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
 YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?  
 YES  NO   
*If "NO," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
 N/A  YES  NO   
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".  
 If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:  
 a) Approved in a 505(b)(2) application?  
 YES  NO   
*If "YES", please list which drug(s).*  
 Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?  
 YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES  NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The proposed drug (glycerol phenylbutyrate) is a prodrug of an approved drug (sodium phenylbutyrate)

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.*

*If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): generic sodium phenylbutyrate

<b>PATENT CERTIFICATION/STATEMENTS</b>
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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JESSICA M BENJAMIN  
01/31/2013



## MEMORANDUM

Office of Pediatric Therapeutics  
Office of the Commissioner  
10903 New Hampshire Ave, WO32-5126  
Silver Spring, MD 20993-002  
Tel (301) 796-8665; FAX (301) 847-8619

**Date:** January 11, 2013

**From:** Michelle D. Roth-Cline, M.D., Ph.D., Pediatric Ethicist  
Robert M. Nelson, M.D., Ph.D., Deputy Director/Senior Pediatric Ethicist  
Office of Pediatric Therapeutics, OC

**Through:** M. Dianne Murphy, M.D., Director  
Office of Pediatric Therapeutics, OC

**To:** Nancy Snow, M.D., Medical Officer  
Division of Gastrointestinal and Inborn Errors Products, CDER

**Re:** **NDA 203, 284: Ravicti for Urea Cycle Disorders in Infants**

**Materials Reviewed**

- 1) Ethics consult request from Nancy Snow, M.D., dated December 7, 2012
- 2) Hyperion response to August 13, 2012 Information Request from FDA
- 3) Hyperion response to December 5, 2012 Information Request from FDA

**Background**

Glycerol phenylbutyrate (HPN-100 or Ravicti) is an oral pre-pro nitrogen scavenging drug under NDA review for the chronic management of Urea Cycle Disorders (UCDs). UCDs result in high ammonia levels which cause death if untreated. Infants presenting acutely with UCD are placed on intravenous Ammonul (sodium phenylacetate and sodium benzoate) and generally require invasive monitoring (e.g. arterial lines) and intensive care to stabilize. Such infants then are carefully transitioned from intravenous Ammonul to standard oral therapy with Buphenyl (sodium phenylbutyrate). Buphenyl is the only available oral therapy marketed for the chronic management of UCDs. It differs from Ravicti in that it carries a high sodium load, a high pill (powder) burden, and is particularly unpalatable. The active moiety (phenylbutyrate) is the same for both oral drugs.

Because Ravicti contains 3 moles of phenylbutyrate joined to glycerol in an ester linkage, hydrolysis of the ester bond is required to free the phenylbutyrate for absorption. Once freed, absorption and metabolism is identical to that of phenylbutyrate delivered as sodium phenylbutyrate. According to studies performed by the sponsor, pancreatic lipases (including pancreatic triglyceride lipase, pancreatic lipase related protein 2 and carboxyl ester lipase) are the primary enzymes involved in releasing absorbable phenylbutyrate from the prodrug Ravicti. As compared with adults, however, the newborn's exocrine pancreas is "immature." Although gastric lipase is present at physiologically significant levels in preterm and newborn human infants, levels may be variable and low compared to adults. The newborn's ability to digest fats generally matures rapidly to normal adult levels during the first two months of life.

Based on this knowledge, Ravicti may be ineffective in the newborn as the level of pancreatic lipase necessary for adequate hydrolysis of Ravicti to the active moiety phenylbutyrate is unknown. No child

under 2 months was included in any of the Ravicti clinical trials, so there are no data on which to assess efficacy in this subpopulation. If an ineffective drug is given to these seriously ill neonates with UCD, the consequences could be life threatening. In addition, such infants may present at community hospitals where there is a lack of sophistication regarding the management of UCDs. Specifically, the need for hydrolysis of Ravicti into phenylbutyrate may not be appreciated, resulting in an inappropriate substitution of Ravicti for Buphenyl based on ease of administration absent careful monitoring of an infant's therapeutic response. Therefore, although data regarding the efficacy of Ravicti in infants less than 2 months of age are necessary, the Division is considering contraindicating the drug in this vulnerable population until such a study can be performed.

The sponsor has proposed a post marketing trial in which they will study the efficacy of Ravicti in this vulnerable population. The Division would like to make such a study a post-marketing requirement. The Division believes that it may be ethically possible to conduct such a study in the contraindicated population because the enrolled neonates can be intensively monitored as they are switched from intravenous therapy to Ravicti.

### **Question**

The Division is asking whether (1) their rationale for contraindicating a drug while compelling the sponsor to study it in the same population of patients for whom it is contraindicated is rational from an ethical perspective; and (2) if IRBs would agree to conduct such a study. In essence, both concerns are addressed by answering the question of whether such a study would be approvable under 21 CFR 50 subpart D, the additional safeguards for children in research.

### **Response and Recommendations**

In our view, there is no *prima facie* conflict between contraindicating a drug in a particular population and simultaneously subjecting the drug to careful study in the same population. The contraindication is necessary because it is unclear how much pancreatic lipase activity is needed to convert the prodrug into the active moiety, and whether infants less than 2 months of age produce sufficient enzyme to render the product efficacious in this population. Thus, the rationale for the contraindication and the scientific need for further clinical study are the same. The apparent inconsistency between these two actions can be addressed by carefully communicating the rationale for the contraindication in the pediatric use section (8.4) of the product label. The label in this case serves the purpose of informing the public about FDA's concerns, as well as ongoing plans to determine safety and efficacy in infants less than 2 months of age. If others within the Agency question whether a product may be simultaneously studied and contraindicated, a reasonable alternative may be to place a black box warning in the Ravicti label stating that the product should only be used within FDA-regulated clinical trials in children less than 2 months of age, along for the rationale for the warning.

For a clinical study of the efficacy of Ravicti in infants less than 2 months of age to be approvable under 21 CFR 50.52, the risk must be justified by the anticipated benefit to the infants and the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches. Whether any given protocol meets these criteria requires a careful assessment of the exact details of the design and implementation of the study. Two concerns were identified in our discussion with the Division. First, as noted earlier, intensive care and invasive monitoring are necessary to determine whether infants are able to transition safely from intravenous to

oral therapy for their UCDs. It would be inappropriate to subject an infant with a UCD who no longer requires intensive monitoring to the risks of reinitiating such monitoring (e.g., placement of arterial or central catheters to monitor serum ammonia levels). Therefore, the transition from standard therapy (whether intravenous or oral) to Ravicti in the proposed study must be made while enrolled infants still require invasive monitoring and intensive care. Second, we discussed whether enrolled infants should be transitioned directly from intravenous therapy to Ravicti, or whether such infants should be transitioned from intravenous therapy to Buphenyl and then to Ravicti. From our perspective, we believe there is no greater risk to infants in a closely monitored environment to be transitioned from intravenous therapy directly to Ravicti as long as appropriate intravenous rescue therapy is provided as needed to the enrolled infants. However, this judgment requires a careful assessment of the transition and monitoring plan in the proposed protocol. For this reason, we recommend that the Division review the sponsor's proposed protocol prior to implementation, and we can provide further input into this assessment upon request.

Finally, the primary question that the study should address is whether the drug has the intended effect in the enrolled subject population (i.e., the feasibility of transitioning to Ravicti). As such, an open label design with a limited number of infants less than 2 months of age may be sufficient to answer this question. We acknowledge that the decision regarding whether to indicate the drug in infants less than two months of age may be complex if either the enrolled population does not include younger neonates (e.g., 1-2 weeks of age) and/or the success rate of the transition is less than 100%. We ask that the Division update us as appropriate regarding the status of this product. In addition, we look forward to being consulted again at the discretion of the Division as development of this product progresses.

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/s/  
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MICHELLE ROTH-CLINE  
01/11/2013

ROBERT M NELSON  
01/11/2013

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: October 18, 2012

Reviewer(s): Anne Crandall Tobenkin, PharmD.  
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD., M.S.  
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD., MPH  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh.  
Division of Medication Error Prevention and Analysis

Drug Name(s): Ravicti (Glycerol Phenylbutyrate) Liquid 1.1 g/mL

Application Type/Number: NDA 203284

Applicant/sponsor: Ucyclid Pharma Inc.

OSE RCM #: 2012-71

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' evaluation of the container labels, carton, and insert labeling for Ravicti (Glycerol Phenylbutyrate) Liquid (NDA 203284) for areas of vulnerability that could lead to medication errors.

### 1.1 PRODUCT INFORMATION

The following product information is provided in the December 23, 2011 supplement.

- Established Name: Glycerol Phenylbutyrate
- Indication of Use: Adjunctive therapy for chronic management of adult and pediatric patients (greater than 6 years of age) with urea cycle disorders involving deficiencies of enzymes
- Route of administration: Oral
- Dosage form: Liquid
- Dose:
  - Adult dose: 5 g/m<sup>2</sup>/day to 12.4 g/m<sup>2</sup>/day divided into 3 equal doses
- How Supplied: 25 mL, 120 mL, 450 mL bottles
- Storage: Room temperature
- Container and Closure systems: Glass bottles with (b) (4) cap

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 23, 2011
- Carton Labeling submitted December 23, 2011
- Insert Labeling submitted December 23, 2011

## 3 RECOMMENDATIONS

The proposed labels and labeling introduce vulnerability that can lead to medication errors due to incongruent units of measure between the strength and dosing recommendations. Additionally, we request label and labeling revisions to increase the safe use of the product.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

We recommend the following revisions be implemented prior to the approval of this NDA:

**A. General Comments**

1. The container labels express the strength in terms of mL and provide the equivalent gram in parenthesis. We recommend dosing the product in grams as formulations or dosage forms can vary (solution to tablet) therefore, prescribers should prescribe in grams and the pharmacist can translate the dose from grams to mL for the patient. The package insert should also be dosed in terms of gram followed by the mL equivalent dose in parenthesis.

**B. Insert Labeling**

1. The dosing instructions in the Dosage and Administration (Highlights and Section 2) present the recommended dose as the total daily dose, which is then to be divided equally by three. We recommend the instructions include the actual dose per administration to avoid confusion or possible calculation errors.

**C. Container Labels (All Sizes)**

1. Relocate the storage information and “Keep out of reach of children” to the back panel.
2. Relocate the dosage form, “Liquid” so that it appears beneath the established name.
3. Relocate the strength statement so that it appears below the dosage form and increase the prominence of the statement by using larger font.
4. Relocate the Med Guide statement so that it appears below the strength statement and utilize a larger font so that the statement is more prominent.
5. Increase the prominence of the statement “For oral use only” and relocate the statement to the principal display panel.
6. Relocate the “each mL” statement on the principal display panel so that it appears on the side panel.
7. Include a “Usual dose statement” on the container label.

**D. Container Label (Only 25 mL size)**

1. Include the dosage form, ‘Liquid’ on the principal display panel, beneath the established name.
2. Include the statement, ‘For oral use only’ on the principal display panel.

3. Relocate the manufacturer information to the side panel to allow more space for the dosage form and route of administration, as mentioned above.

***E. Carton Labeling***

1. See comments C3-C4.
2. Increase the prominence of the “For oral use only” statement.
3. The carton labeling do not communicate the need for an oral dosing device, however due to the wide range of mL’s that can be calculated to achieve the prescribed dose, we recommend a statement on the carton labeling that communicates to healthcare practitioners the need to dispense a dosing device that best accommodates the dose prescribed.

If you have further questions or need clarifications, please contact Nitin Patel, OSE Project Manager, at 301-796-5412.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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LUBNA A MERCHANT  
10/18/2012

KELLIE A TAYLOR  
10/18/2012

CAROL A HOLQUIST  
10/18/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

DATE: September 20, 2012

TO: Jessica Benjamin, Senior Regulatory Health Project Manager  
Tamara Johnson, Medical Officer,  
Nancy Snow, Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Khairy Malek, M.D., PhD  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-284

APPLICANT: Ucylyd Pharma (Agent Hyperion Therapeutics)

DRUG: Ravicti™ (glycerol phenylbutyrate, HPN-100)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Adjunctive therapy for chronic management of adults and pediatric patients  $\geq 6$

years of age with urea cycle disorders involving deficiencies of the following enzymes: the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (hyperornithinemia–hyperammonemia–homocitrullinuria [HHH] syndrome, also referred to as ornithine translocase deficiency)

Consultation Request Date: February 17, 2012

Inspection Summary Goal Date: September 18, 2012

PDUFA Date: October 23, 2012

## **I. BACKGROUND:**

The sponsor submitted NDA 203-284 for HPN-100 for the indication of treatment of Urea Cycle Disorders (UCDs). UCDs are inborn errors of metabolism that can result from decreased or absent activity of any of the following enzymes: carbamyl phosphate synthetase (CPS), N-acetylglutamine synthetase (NAGS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), or arginase (ARG). These disorders prevent the conversion of waste nitrogen into urea and result in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. The age of onset is often in the neonatal period, but can occur at any age, depending on the severity of the disorder. Therapeutic strategies for patients with UCDs are aimed at both reducing the requirement for ureagenesis and exploiting other pathways for the synthesis and excretion of other waste nitrogen products. This includes dietary protein restriction, arginine or citrulline supplementation, and use of nitrogen-scavenging drugs.

Sodium phenylbutyrate (NaPBA) tablets and powder have been approved in the US since 1996 (trade name Buphenyl) as an adjunctive therapy in the long-term management of patients with UCDs. The study drug, HPN-100 (glyceryl tri-(4-phenylbutyrate, GT4P), a pro-drug of PBA (phenylbutyrate) is expected to provide similar or superior nitrogen-scavenging ability, while eliminating the current issues of bad taste, odor, high sodium content, and pill burden. NaPBA was clinically shown to be effective in long-term survival in patients with UCDs reducing the incidence of deaths due to hyperammonemic encephalopathy.

HPN-100 is a precursor of PBA which is released from HPN-100 in the gastrointestinal tract and acts as a nitrogen-scavenging agent in the body. PBA is a precursor of the active agent PAA (phenylacetate), which combines with glutamine to form PAGN, which is excreted in urine. Phase 2 studies demonstrated that HPN-100 is well tolerated and exhibits a similar safety profile to NaPBA. Venous ammonia levels were generally lower with HPN-100 compared to NaPBA. Fifteen (15) AEs were reported in 5 subjects on HPN-100.

The review division requested inspection of three investigators that participated in the conduct of the following three protocols in the support of data for licensure:

1. Protocol UP 1204-003: “A Phase 2, Open-Label, Switch-Over, Dose-Escalation Study of the Safety and Tolerability of Hpn-100 (Glyceryl Tri [4-Phenylbutyrate]) Compared to Buphenyl<sup>®</sup>(Sodium Phenylbutyrate) in Patients with Urea Cycle Disorders”

2. Protocol HPN-100-005: “A Phase 2, Fixed-Sequence, Open-Label, Switch-Over Study of the Safety and Tolerability of HPN-100 Compared to Sodium Phenylbutyrate in Children 6-17 Years of Age with Urea Cycle Disorders, with a Long-Term Safety Extension” and
3. Protocol HPN-100-006: “A Phase 3, Randomized, Double-Blind, Cross-Over, Active-Controlled Study of the Efficacy and Safety of HPN-100, Glyceryl Tri-(4-phenylbutyrate), for the Treatment of Adults with Urea Cycle Disorders.”

The three clinical sites selected for inspection enrolled 50% or more of the patient population of the above listed efficacy trial protocols.

## II. RESULTS (by Site):

Name of CI	Site #, Protocol # and # of Subjects	Inspection Date	Final Classification
Brendan Lee, M.D., Ph.D. Department of Molecular and Human Genetics One Baylor Plaza Room 814 Houston, TX 77030	Site # 01 HPN-100-006, 7 Subjects UP 1204-003, 6 Subjects	May 14 to June 15, 2012	VAI (Preliminary)
George Diaz, M.D., Ph.D. Mount Sinai School of Medicine Department of Genetics and Genomic Sciences One Gustave L. Levy Place New York, NY 10029	Site # 05 HPN-100-006, 9 Subjects HPN-100-005, 2 Subjects UP 1204-003, 3 Subjects	April 26 to May 9, 2012	NAI
William Rhead, M.D., Ph.D. Children’s Hospital of Wisconsin Genetics Center 9000 West Wisconsin Ave Milwaukee, WI 53226	Site #03 HPN-100-006, 3 Subjects HPN-100-005, 3 Subjects UP 1204-003, 4 Subjects	April 23 to May 3, 2012	VAI (Preliminary)

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Brendan Lee, M.D. Site # 01  
Houston, TX 77030

- a. **What was inspected:** At this site, 2 protocols were conducted, Protocol UP1204-003 and Protocol HPN-100-006. For Protocol UP 1204-003, six subjects were screened and four subjects completed the study. One subject was discontinued and another was screened twice. For Protocol HPN-100-006, seven subjects were enrolled and all completed the study. The field investigator reviewed all the records including: informed consent forms, inclusion/exclusion criteria, CRFs, diet records, drug accountability, and adverse events. The venous ammonia results were available at the site and were verified against the data listings.
- b. **General observations/commentary:** The venous ammonia results for all subjects' study visits were available at the site and were verified against the data listings from the NDA submission that were provided to the FDA field investigator. A Form FDA 483 was issued. Violations observed were failure to report the following adverse events for Protocol UP 1204-003: bloating for Subject 001, headache for Subjects 001 and 004. For Protocol HPN-100-006, Subject 006 developed a small papular lesion on the chest and 2 small papules on the back during physical examination at V6. This was diagnosed as Herpes Zoster, but was not recorded as an adverse reaction. Another violation was that none of the study subjects were switched over gradually to the 100% GT4P treatment based on the prescribed dose of phenylbutyric acid equivalents.
- c. **Assessment of data integrity:** The observations noted above do not affect the validity of the data. Data generated at this site can be used in support of the NDA.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon review of the EIR.

2. George Diaz, M.D., Site # 05  
New York, NY 10029

- a. **What was inspected:** At this site 3 protocols were conducted: UP 1204-003, HPN-100-005 and HPN-100-006. For Protocol UP 1204-003, three subjects were screened and enrolled, one subject withdrew and two subjects completed the study. For Protocol HPN-100-005, two subjects were enrolled and completed the study. For Protocol HPN-100-006, nine subjects were enrolled and completed the study. The FDA field investigator reviewed all the study records for informed consent forms, medical records, drug accountability records, and adverse events.
- b. **General observations/commentary:** A comparison between the source documents and the data listings provided with the assignment found no

discrepancies. No significant regulatory violations were recorded.

- c. **Assessment of data integrity:** The study was adequately conducted and the data generated at this site can be used in support of the NDA.

3 William Rhead, M.D. Site # 003  
Milwaukee, WI 53226

- a. **What was inspected:** At this site three protocols were conducted: Protocol UP 1204-003, Protocol HPN-100-005, and Protocol HPN-100-006. In Protocol UP 1204-003, four subjects were screened, three subjects were enrolled, and two subjects completed the study. In Protocol HPN 100-005, three subjects were enrolled, but one withdrew prior to completion of the extension. In Protocol HPN 100-006, three subjects were screened and two subjects were enrolled. The FDA field investigator reviewed the records of all the subjects including source documents, medical records, CRFs, laboratory values, and drug accountability records.
- b. **General observations/commentary:** The inspection revealed two protocol violations. For Protocol UP 1204-003, a serious adverse reaction occurred to Subject # 03-001 on June 18, 2008 for Visit 2-1 with a pre-dose ammonia level of 161. The report was sent to the sponsor, a week later on 6/25/08, not within 24 hours as required by the protocol. The CI suggested that the major contributing factors were missing two doses of both Buphenyl and arginine the day prior to the visit and to increased protein intake. The subject was treated for hyperammonemia and monitored until stable.

For Protocol HPN 100-005, the site failed to obtain spot PK and urine analysis for Subject #03-031 at the Month 5 Visit and for Subject #03-033 at the Month 3 Visit as required by the protocol in effect at that time. The protocol was amended later by the IRB and this requirement was removed.

- c. **Assessment of data integrity:** These violations will not affect the validity of the data. The data generated at this site can be used in support of the NDA.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon review of the EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites were selected for inspection for the clinical trials submitted in support of this NDA. The inspection of Dr. Diaz's, site was classified as NAI. The inspections of

Drs. Lee's and Rhead's sites were classified as VAI; however, the nature of the violations does not significantly impact data reliability. The data from the three sites are reliable and can be used in support of the NDA.

Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon review of the EIR.

*{See appended electronic signature page}*

Khairy Malek, M.D., Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Susan Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KHAIRY W MALEK  
09/20/2012

SUSAN LEIBENHAUT  
09/20/2012

SUSAN D THOMPSON  
09/20/2012

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	203284
<b>Generic Name</b>	Ravicti (glycerol phenylbutyrate), HPN-100
<b>Sponsor</b>	Hyperion Therapeutics
<b>Indication</b>	Adjunctive therapy for chronic management of adults and children (6-17 years of age) with urea cycle disorders (UCD)
<b>Dosage Form</b>	Orally liquid form
<b>Drug Class</b>	Nitrogen scavenger
<b>Therapeutic Dosing Regimen</b>	4.5 mL/m <sup>2</sup> /day to 11.2 mL/m <sup>2</sup> /day (5.0 g/m <sup>2</sup> /day to 12.4 g/m <sup>2</sup> /day). Total daily dose is not to exceed 17.5 mL (19.3 g)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	6.6 g t.i.d. (19.8 g/day)
<b>Submission Number and Date</b>	23 Dec 2011
<b>Review Division</b>	DGEIP

**1 SUMMARY**

**1.1 COMMENTS FROM QT-IRT TO THE REVIEW DIVISION**

We do not believe assay sensitivity had been successfully demonstrated in this study (see below for details). Therefore, QT-IRT suggests a PMR for further evaluation of the cardiovascular safety for the study drug.

**1.2 OVERALL SUMMARY OF FINDINGS**

The study was inconclusive. Even though the largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, the moxifloxacin time profile was not consistent with the expected moxifloxacin time course. We do not expect to see moxifloxacin peaks at 0.5 h post-dose after a single oral dose of 400 mg was administered (Figure 4). Therefore, we do not believe assay sensitivity has been demonstrated in this study.

Based on the double delta analysis for the study drug, it appears that no significant QTc prolongation effect of HPN-100 (13.2 g/day and 19.8 g/day) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between HPN-100 (13.2 g/day and 19.8 g/day) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

In this randomized, blinded crossover study, 40 healthy subjects received HPN-100 13.2 g/day, HPN-100 19.8 g/day, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HPN-100 (13.2 g/day and 19.8 g/day) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
HPN-100 13.2 g/day,	1.5	-2.8	(-5.0, -0.7)
HPN-100 19.8 g/day,	12	-3.4	(-5.5, -1.3)
Moxifloxacin 400 mg*	2	9.5	(7.0, 11.9)

\* Multiple endpoint adjustment of 3 time points was applied.

HPN-100, the prodrug, likely gets completely digested by pancreatic lipases to release PBA and intact HPN-100 has not been detected in the systemic circulation after dosing. After 3 days of continued dosing, the suprathreshold dose of HPN-100 (19.8 g/day administered as t.i.d.) produces mean  $C_{max}$  values that are 1.6-fold, 2.5-fold and 1.5-fold the mean  $C_{max}$  for therapeutic dose (13.2 g/day administered as t.i.d.) for drug metabolites 4-phenylbutyric acid (PBA), phenylacetic acid (PAA) and phenylacetylglutamine (PAGN) respectively. The concentrations with suprathreshold dose cover the range of exposures of all three metabolites in UCD patients seen across 3 trials, 2 involving adults (UP-1204-003 phase 2 study, HPN-100-006 phase 3 study) and 1 involving pediatric patients (HPN-100-005 phase 2 study). However the suprathreshold dose does not cover the theoretical worst case scenario that can occur in hepatic impairment patients as a result of the following three factors:

- the proposed highest dose to be approved ( $(b) (4)$  g/day) is similar to the suprathreshold dose studied in the QT study (19.8 g/day),
- hepatic impairment results in ~2-fold increase in  $C_{max}$  for PAA,
- $(b) (4)$  is proposed for hepatic impairment in the label.

It is possible that such a clinical scenario may not arise since the dose is titrated up to the maximum value based on the efficacy and tolerability and arm 1 of QT study has shown that exposures for doses above the current selected suprathreshold dose results in tolerability issues (nausea, headache, dizziness) leading to discontinuations. Within the studied metabolite concentrations which cover the range of exposures observed in UCD patients, there are no detectable prolongations of the QT-interval. PAGN, a metabolite formed from PAA in the transformation process from HPN-100 to PBA and then to PAA, gets excreted renally. But the role of renal impairment on drug/metabolites exposure has not been studied. The effect of other drug-drug interactions on HPN-100 and metabolite exposures is not known at this time.

In arm 2 of the thorough QT study, ECG measurements were collected frequently only in the early part of the day 3 while the measurements were sparse (8, 12, and 16 h) around the day's peak concentrations of metabolites (12 h from the time of first dose of day 3).

Thus the sampling scheme was sub-optimal to detect changes in the QT interval at daily maximum drug metabolite concentrations.

## **2 PROPOSED LABEL**

### **2.1 SPONSOR PROPOSED LABEL**

Sponsor proposed the following language in the package insert:



### **2.2 QT-IRT RECOMMENDED LABEL**

*We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.*

#### **12.2 ECG Effects**

The effect of multiple doses of Ravicti 13.2 g/day and 19.8 g/day on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm crossover study in 40 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) for Ravicti was below 10 ms, the threshold for regulatory concern. However, assay sensitivity was not established in this study. Therefore, a small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out. The 19.8-g/day dose utilized in this study is the highest intended clinical dose.

## **3 BACKGROUND**

### **3.1 PRODUCT INFORMATION**

HPN-100 (Glyceryl tri-(4-phenylbutyrate) (GT4P)) a triglyceride containing three molecules of 4-phenylbutyric acid (PBA) linked to a triglyceride backbone. It is a prodrug of PBA and pre-prodrug of phenylacetate (PAA), the active metabolite. HPN-100 shares the same mechanism of action and metabolic pathway as the marketed product sodium phenylbutyrate (European Union [EU] trade name: AMMONAPS®; United States [US] trade name: BUPHENYL®), but HPN-100 provides a unique delivery modality-formulation to provide the active metabolite, PAA. Sodium phenylbutyrate was approved in the US in 1996 and in the EU in 1999.

### **3.2 MARKET APPROVAL STATUS**

HPN-100 is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

From eCTD 2.4

“The potential effects of GPB or its metabolites (PBA and PAA) on cardiovascular function were assessed in vitro and in vivo. In vitro hERG and rabbit cardiac myocyte assays provided an index of the potential risk for a compound to affect the QT interval. For PBA, the inhibition of peak tail currents (IKr) in the hERG assay at a concentration of 894.2 µg/mL was not confirmed in the rabbit cardiac myocyte assay at a higher concentration of 1591.8 µg/mL. These in vitro concentrations of PBA represent a 38- to 68-fold margin relative to the in vivo maximum plasma concentration (C<sub>max</sub>) for PBA (23.3 µg/mL) in the monkey after a single oral dose of 0.6 g/kg of GPB (7.2 g/m<sup>2</sup>).

“In vivo, GPB did not significantly alter blood pressure or heart rate following a single oral dose of 1 g/kg or 4 g/kg in cynomolgus monkeys. The NOAEL for GPB was 1 g/kg for behavioral effects and ≤ 1 g/kg for electrocardiogram (ECG) effects (based on a questionable shortening of the PR interval). A higher dose of 4 g/kg of GPB was associated with adverse clinical signs, shortening of the PR interval, and moderate prolongation of the QRS duration and QTc interval; however, there were no effects on ECG morphology or rhythm at this dose.”

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

“Safety data are provided in 96 patients (of whom 91 received HPN-100) with UCD deficiencies including CPS, OTC, AS, ASL, ARG, or HHH subtypes across four studies (UP 1204-003, HPN-100-005, HPN-100-006, and HPN-100-007). When compared with the estimated 400 UCD patients in the US who are actively treated with NaPBA, this safety database, which includes 65 adult and 26 pediatric patients ages 6–17 years dosed with HPN- 100, is estimated to represent approximately 40% of all adult UCD patients on NaPBA and approximately 20–25% of all pediatric UCD patients ages 6–17 in the US on NaPBA. The safety analysis includes 69 UCD patients (45 adult and 24 pediatric patients 6–17 years of age) who completed the 12-month safety studies.

“Additional safety data are provided in 130 healthy adults (including 32 enrolled in two Phase 1 single- and multiple-dose PK/pharmacodynamic [PD] studies.”

*Reviewer’s comments: No syncope, seizures, sudden cardiac death or ventricular arrhythmias were reported in these studies. No clinically relevant ECG changes were reported.*

## 4 SPONSOR’S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 73480. The sponsor submitted the study report HPN-100-010 for HPN-100, including electronic datasets and waveforms to the ECG warehouse.

## **4.2 TQT STUDY**

### **4.2.1 Title**

“A DOUBLE-BLIND RANDOMIZED CROSSOVER TRIAL TO DEFINE THE ELECTROCARDIOGRAM EFFECTS OF HPN-100 USING A CLINICAL AND A SUPRATHERAPEUTIC DOSE COMPARED TO PLACEBO AND MOXIFLOXACIN (A POSITIVE CONTROL) IN HEALTHY MEN AND WOMEN: A THOROUGH ELECTROCARDIOGRAM TRIAL”

### **4.2.2 Protocol Number**

HPN-100-010

### **4.2.3 Study Dates**

11 May 2010 -- 16 September 2010

### **4.2.4 Objectives**

Primary Objective:

“The primary objective of Arm 2 of this study was to assess the effects of steady-state levels of HPN-100 metabolites (PBA, PAA, and PAGN) on 12-lead ECG parameters in healthy male and female subjects with the primary endpoint being the time-matched change from baseline in the QT interval corrected for HR based on an individual correction method (QTcI).”

Secondary Objectives:

- to evaluate the effects of steady-state levels of HPN-100 metabolites on the change from baseline using QTcB, QTcF, HR, QT, PR, and QRS intervals and ECG morphological patterns,
- to correlate the QTcI change from baseline and the PK of PBA, PAA, and PAGN,
- to examine the effect of gender on the metabolism of HPN-100,
- to assess the general safety and tolerability of HPN-100.

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

This is a double-blind, randomized, single-site, 4-arm crossover placebo- and active-controlled design in healthy male and female subjects.

#### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

#### **4.2.5.3 Blinding**

The study is double-blind with respect to placebo versus HPN-100. The positive (moxifloxacin) control was not blinded.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

“Eighty-six healthy subjects were to receive each of the following 4 treatment regimens for 3 days with a 4-day minimum washout period between treatments, and in a randomized sequence:

Treatment A: Placebo for HPN-100, via syringe orally TID;

Treatment B: Moxifloxacin, 400-mg tablet, single oral dose;

Treatment C: HPN-100, 4 mL via syringe orally TID, 13.2 g/day total, neat, therapeutic dose after resuming Arm 2;

Treatment D: HPN-100, 6 mL via syringe orally TID, 19.8 g/day total, neat, therapeutic dose after Arm 1 and suprathereapeutic dose after resuming Arm 2;”

### 4.2.6.2 Sponsor’s Justification for Doses

Sponsor performed a thorough QTc study of HPN-100. According to the sponsor, “Assuming an R of 2 for PAA in hepatically-impaired patients versus healthy adults as detected in study UP 1204-002, a 2-fold increase in the therapeutic dose should have resulted in plasma metabolite levels of PBA, PAA, and PAGN that equaled or exceeded those anticipated in hepatically-impaired patients receiving the maximum therapeutic dose of HPN-100. In the current study, the clinical (i.e., lower) dose of HPN-100 was anticipated to correspond to 20 g NaPBA, which is approved at 9.9 to 13 g/m<sup>2</sup> in adults (maximum of 20 g) or 450 to 600 mg/kg in children (maximum of 20 g). Each gram of NaPBA is equal to 0.95 g of GPB and 1 mL HPN-100 contains 1.1 g of GPB. Therefore, the dose of HPN-100 delivering a PBA molar equivalent to 20 g NaPBA is 19.1 g GPB or approximately 17.4 mL. However, for the convenience of dosing, the Sponsor planned to use 18 mL HPN-100 (6 mL TID, 19.8 g total dose of GPB) as the therapeutic dose and 200% of the maximum dose of HPN-100 (39.6 g total dose of GPB, 36 mL, or 12 mL TID) as the suprathereapeutic dose. In study UP 1204-003, the highest dose administered was the therapeutic dose of 17.4 mL HPN-100 (5.8 mL TID, 19.1 g/day). HPN-100 administered at 200% of the therapeutic dose had not been evaluated to date. Therefore, Arm 1 of the current study determined the safety and tolerability of a 1.5- and 2-fold higher dose (27 mL [9 mL TID, 29.7 g/day] and 36 mL [12 mL TID, 39.6 g/day], respectively) to establish the suprathereapeutic dose used in Arm 2, the thorough QTc study. Because of tolerability issues during Period 1 of Arm 2 (including headache, nausea, dizziness, and emesis, leading to subject discontinuation), the Sponsor restarted Arm 2 using 18 mL HPN-100 (6 mL TID, 19.8 g total dose of GPB) as the suprathereapeutic dose and 67% of the suprathereapeutic dose of HPN-100 (13.2 g total dose of GPB, 12 mL, or 4 mL TID) as the therapeutic dose. The clinical dose of HPN-100 was redefined above as 4 mL TID (13.2 g/day), and the suprathereapeutic dose was chosen as 6 mL TID (19.8 g/day). The suprathereapeutic dose used in Arm 2 was lowered based on the safety and tolerability data obtained in Arm 1 and Arm 2, Period 1. The revised dose was determined by an independent review group assembled by (b) (4) along with the Investigator’s clinical judgment at the Sponsor’s request. Note that the therapeutic dose utilized in this study is very similar to the average dose received by the 44 adult UCD subjects (mean 14 g) of NaPBA per day, equivalent to 13.5 g of HPN-100

per day, who completed the pivotal efficacy study (HPN-100-006). Additionally, the suprathereapeutic dose is 50% greater than the dose of 13.2 g/day being used in the protocol HPN-100-008 for hepatic encephalopathy and yielded average metabolite concentrations greater than those observed during open label dosing with 13.2 g/day in Part A of protocol HPN-100-008.”

*Source: section 9.4.4 in sponsor’s study report*

*Reviewer’s Comment: FDA, in its protocol review, had recommended using 19.1 g of the drug (equivalent to 20 g NaPBA) as the therapeutic dose while sponsor has used this amount as the suprathereapeutic dose in the current thorough QT study. The selected suprathereapeutic dose of HPN-100 (19.8 g/day administered as t.i.d.) produces mean  $C_{max}$  values that are 1.6-fold, 2.5-fold and 1.5-fold the mean  $C_{max}$  for therapeutic dose (13.2 g/day administered as tid) for drug metabolites PBA, PAA and PAGN, respectively. The concentrations with suprathereapeutic dose cover the range of exposures of all three metabolites in UCD patients across the three adult/pediatric trials (UP-1204-003, HPN-100-006, HPN-100-005). However the suprathereapeutic dose does not cover the theoretical worst case scenario that can occur in hepatic impairment patients as a result of a combination of following three factors:*

- *the proposed highest dose to be approved ( (b) (4) g/day) is almost equal to the suprathereapeutic dose studied in the QT study (19.8 g/day),*
- *hepatic impairment results in doubling the  $C_{max}$  for PAA,*
- *(b) (4) is suggested for hepatic impairment in the label.*

*It is possible that such a clinical scenario may not arise since the dose is titrated to the maximum value based on efficacy and tolerability and arm 1 of QT study has shown that exposures for doses above the current suprathereapeutic dose results in tolerability issues (nausea, headache, dizziness) leading to discontinuations. Thus the proposed suprathereapeutic dose seems to be reasonable with the caveat that it may not cover the exposures in patients with hepatic impairment if they are exposed to the proposed highest dose mentioned in the label. PAGN, a metabolite formed from PAA in the transformation process from HPN-100 to PBA and then to PAA, gets excreted renally. But the role of renal impairment on drug/metabolites exposure has not been studied.*

#### **4.2.6.3 Instructions with Regard to Meals**

All doses were to be administered 3 times a day with meals. Meals were timed as follows: breakfast, lunch, and dinner were served at 0.25, 5 ± 0.25, and 10 ± 0.25 h after the first dose of the day, respectively.

*Source: Section 9.4.5 and 9.4.9 in sponsor’s study report*

*Reviewer’s Comment: Based on a single dose fed-fasting study of Ravicti in 8 healthy volunteers Ravicti is at least as bioavailable when administered with food as it is fasting. Thus, dosing with food is acceptable.*

#### **4.2.6.4 ECG and PK Assessments**

**ECG assessment:**

“Digital ECGs were obtained on Day 1 at -45, -30, and -15 minutes before the first dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23 h after the first dose on Day 3. Electrocardiogram extractions were performed before blood collections.”

**PK assessment:**

“Blood samples for PK analysis were collected on Day 1 predose and Day 3 at predose (trough level) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23 h after the first dose of the day.”

*Source: Footnotes to Table 9-4 in sponsor’s study report*

*Reviewer’s Comment: In arm 2 of the thorough QT study, ECG measurements were collected frequently only in the early part of the day 3 to monitor the effects of peak concentration of metabolites (around 4-6 h) after first HPN-100 dose of the day while the measurements were sparse (8, 12, and 16 h) around the day’s peak concentrations of metabolites (12 h from the time of first dose). Thus the sampling scheme was sub-optimal to detect changes in the QT interval at daily maximum drug metabolite concentrations (Figure 1).*

**4.2.6.5 Baseline**

ECG measures before dose on the treatment day were used as baseline.

**4.2.7 ECG Collection**

“ECGs were obtained digitally using a Mortara Instrument (Milwaukee, Wisconsin) H12+ ECG continuous 12-lead digital recorder, which obtained ECGs on Day 1 (predose) and Day 3 (postdose) of each arm of the crossover. The ECGs were stored continuously on a flash card and were not available for review until the card was received by the central ECG laboratory, eRT, and analyzed. Electrocardiograms used in the analysis were selected by predetermined time points, as detailed below, and were analyzed centrally using a high resolution manual on-screen caliper semi-automatic method with annotations.

“Electrocardiograms were sent to a central laboratory, eRT, for a treatment-blinded, high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

“The primary lead for interval measurements was Lead II. However, if technical issues or unstable HR existed, a secondary lead was Lead V5. A tertiary lead, Lead V2, could have been used when severe technical issues or unstable HR existed in the primary or secondary lead, followed by the most appropriate lead, if necessary. Electrocardiogram readers were blinded to subject identifiers, treatment, and visit. All ECGs for a given subject were analyzed by the same reader. Quality Assurance reports for inter- and intra-observer variability were produced by the central ECG laboratory and provided to the Sponsor.”

**4.2.8 Sponsor’s Results**

**4.2.8.1 Study Subjects**

Demographics and other baseline characteristics are summarized in Table 2

**Table 2: Demographics**

Demographic	Summary Results
Mean age (range) in years	28 (18 to 45)
Mean weight (range) in kg	72.1 (51.2 to 94.0)
Mean height (range) in cm	170.8 (155.0 to 197.6)
Mean BMI (range) in kg/m <sup>2</sup>	24.6 (19.2 to 29.7)
Gender (n[%])	
Male	47 (54.7%)
Female	39 (45.3%)
Ethnicity (n[%])	
Hispanic or Latino	5 (5.8%)
Not Hispanic or Latino	81 (94.2%)
Race (n[%])	
White	60 (69.8%)
Black or African American	20 (23.3%)
Asian	2 (2.3%)
Other	4 (4.7%)

Source: [Table 14.1-2b](#).

Source: *Table 11-2, CSR*

#### 4.2.8.2 Statistical Analyses

##### 4.2.8.2.1 Primary Analysis

The time-matched analysis was conducted as the primary endpoint as recommended by ICH E14. Table 11-13 details the 2-sided 90% or the equivalent 1-sided 95% upper confidence boundary in ms for each treatment at each time point showing the placebo and baseline-corrected (delta delta) analysis for each of the moxifloxacin and HPN-100 dose groups.

**Table 3: Placebo-Corrected Change from Baseline-Estimates (Sponsor's Results)**

Time (hr)	HPN-100 13.2 g/d (n=66)			HPN-100 19.8 g/d (n=60)			Moxifloxacin 400 mg (n=69)		
	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
0.5 hour	-4.0	-6.4	-1.7	-5.4	-7.8	-2.9	8.6	5.5	11.7
1 hour	-3.2	-5.5	-0.8	-5.0	-7.5	-2.5	8.8	5.8	11.9
1.5 hour	-2.8	-5.1	-0.4	-4.1	-6.6	-1.6	8.1	5.0	11.2
2 hour	-3.2	-5.6	-0.8	-4.3	-6.8	-1.8	9.5	6.4	12.5
2.5 hour	-4.4	-6.8	-2.0	-5.6	-8.1	-3.2	7.4	4.3	10.5
3 hour	-5.9	-8.3	-3.6	-7.1	-9.6	-4.6	6.9	3.7	10.0
4 hour	-5.6	-7.9	-3.2	-6.5	-9.0	-4.1	7.8	4.7	10.9
6 hour	-4.0	-6.3	-1.6	-5.7	-8.2	-3.2	5.8	2.7	8.9
8 hour	-5.1	-7.5	-2.8	-4.2	-6.7	-1.7	6.0	2.9	9.1
12 hour	-2.9	-5.2	-0.5	-3.4	-5.9	-0.9	4.5	1.4	7.6
16 hour	-7.1	-9.5	-4.8	-8.2	-10.7	-5.7	6.7	3.6	9.8
23 hour	-4.7	-7.1	-2.4	-6.6	-9.1	-4.1	5.4	2.3	8.4
Time Average	-4.4	-6.2	-2.6	-5.5	-7.4	-3.7	7.1	5.3	8.8

Source: CSR Table 11-13

#### 4.2.8.2.2 Assay Sensitivity

The same time-averaged analysis was done for moxifloxacin. The largest lower bound was 6.4 ms.

“The moxifloxacin group met the assay sensitivity criteria outlined in the statistical plan, with the 1 and 2 hour time points exceeding the threshold mean of  $\geq 5$  msec, which met the expected profile with the mean change of 5 to 10 msec and upper CIs of 8 to 13 msec.”

*Reviewer's Comments: Our independent analysis is provided in section 5.2.*

#### 4.2.8.2.3 Categorical Analysis

“The outlier analysis was exploratory only since there was little power to detect individuals that are genetically sensitive to potential QT-prolonging drugs in a small sample size in healthy volunteers. Nevertheless, the specific outlier criteria were a new abnormal U wave, new  $> 500$  msec absolute QTc duration, and a  $> 60$  msec change from baseline.

“For QTcI, there were no occurrences in these numeric criteria for the HPN-100 dose groups (clinical or suprathreshold doses). The nonspecific outlier criterion was a 30 to 60 msec change from baseline, which for QTcI showed 1 subject on placebo, 2 subjects on moxifloxacin, and no subjects on either HPN-100 13.2 or 19.8 g/day.”

### 4.2.8.3 Safety Analysis

Approximately twice as many AEs were reported following 6 mL HPN-100 (129) compared with placebo (62), and an intermediate number (83) was reported with 4 mL HPN-100. The fewest number was reported with moxifloxacin (52), which was administered as a single dose on Day 3 rather than TID for 3 days.

Fifty-one of 77 subjects reported a total of 190 treatment-related AEs; most of these (100/190 [53%]) occurred at 6 mL HPN-100. Among these 77 subjects, 51 subjects (66%) had at least 1 treatment-related (possibly or probably related) AE, including 34% of subjects on 4 mL HPN-100 and 55% of subjects on 6 mL HPN-100. The only treatment related AEs occurring in  $\geq 5\%$  of HPN-100 treated subjects were headache (54%), nausea (28%), dizziness (11%), and abdominal discomfort (7%). All of these treatment-related AEs were more frequent at 6 mL HPN-100 than at 4 mL

There were no deaths and only 1 SAE reported in this study (pneumothorax).

A total of 18 subjects in Arm 2 had AEs resulting in discontinuation of study drug, including 3 subjects on 4 mL HPN-100, 4 subjects each on placebo and 9 mL HPN-100, and 7 subjects on 6 mL HPN-100; all of these subjects were discontinued from the study for 1 or more of these AEs. Nausea and headache were the most frequent AEs leading to discontinuation and occurred in multiple subjects at each HPN-100 dose level as well as placebo (nausea: 4 subjects on 6 mL, 3 subjects on 4 mL, 1 subject on 9 mL, and 1 subject on placebo; headache: 4 subjects on 9 mL, 3 subjects each on 6 mL and placebo; and 2 subjects on 4 mL). Other AEs resulting in discontinuation in more than 1 subject were dizziness in 3 subjects (2 on 9 mL HPN-100, 1 on 6 mL) and abdominal pain, asthenia, and photophobia in 2 subjects each.

*Reviewer's comments: no AEs of concern as per ICH E14 guidance were reported.*

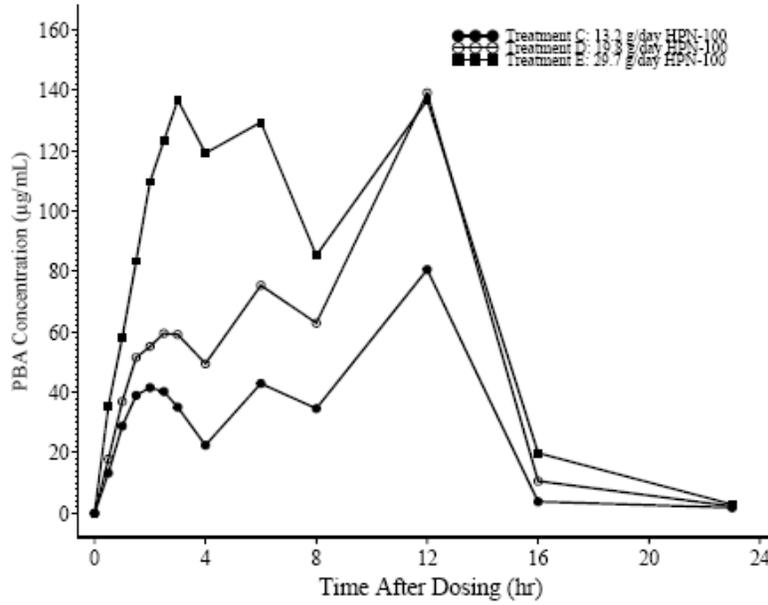
### 4.2.8.4 Clinical Pharmacology

#### 4.2.8.4.1 Pharmacokinetic Analysis

Sponsor's geometric mean concentration-time profiles for HPN-100 metabolites are shown in Figure 1. The PK results for HPN-100 metabolites are presented in Table 4.  $C_{max}$  values in the thorough QT study were 1.6-fold, 2.5-fold and 1.5-fold for drug metabolites PBA, PAA and PAGN, respectively, following administration of 19.8 g/day of HPN-100 suprathreshold dose compared with 13.2 g/day of HPN-100, the intended clinical therapeutic dose.

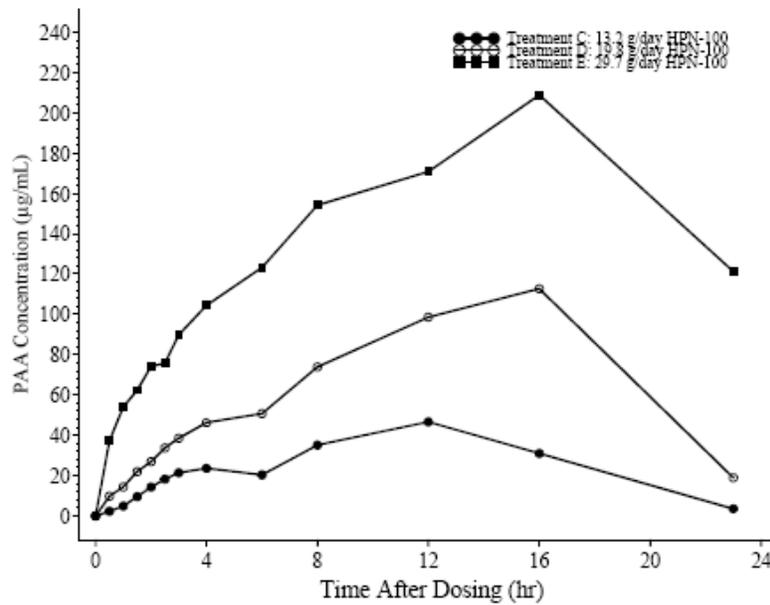
**Figure 1: Sponsor's Geometric Mean Concentration-Time Profiles for metabolites of HPN-100 with supratherepatic (19.8 g/day) and therapepatic (13.2 g/day) dose of HPN-100. The metabolites are: A) PBA, B) PAA and C) PAGN**

A)

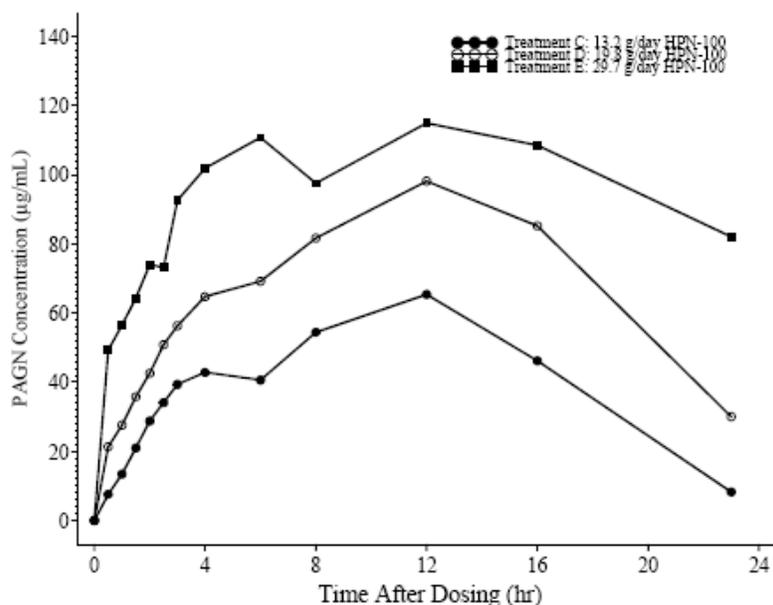


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B)



C)



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Note: Data for Treatment E (29.7 g/day) needs to be ignored in above plots while considering the daily  $T_{max}$  and  $C_{max}$ , since this dose level was not pursued further in the QT study because of tolerance issues.

Source: Figure 14.2.1-3a through Figure 14.2.1-3c in sponsor's study report

**Table 4: Sponsor's Results for Pharmacokinetic Parameters**

	$C_{max}^a$		$C_{max}$ Range <sup>a</sup>		$T_{max}^b$ (hr)	$AUC_{0-23}$		CL/F or CL/Fm		$t_{1/2}$ (hr)	$\lambda_z$ (1/hr)	$V_z/F$ or $V_z/F_m$				
	(µg/mL)	N	(µg/mL)	N		N	(µg-hr/mL)	(µg-hr/mL)	N			(L/hr)	N	(L)	N	
<b>Day 3</b>																
<b>Treatment C</b> (4 mL HPN-100 TID):																
PBA	66.3 (26.3)	19.8, 161	66	2.58 (1.08, 6.22)	66	930 (225)	606, 1311	15	15.0 (3.63)	15	3.88 (2.77)	5	0.246 (0.129)	5	96.9 (73.5)	5
PAA	28.2 (12.5)	7.50, 62.7	66	4.08 (2.08, 6.13)	66	942 (381)	220, 1805	25	14.4 (8.84)	25	NC	0	NC	0	NC	0
PAGN	46.8 (10.5)	28.2, 69.1	66	4.08 (2.08, 6.13)	66	941 (210)	389, 1650	65	23.8 (6.27)	65	NC	0	NC	0	NC	0
<b>Treatment D</b> (6 mL HPN-100 TID):																
PBA	99.9 (35.3)	27.0, 187	69	6.08 (1.12, 8.00)	69	1399 (458)	570, 2074	40	16.2 (6.79)	40	3.85 (2.65)	6	0.266 (0.156)	6	77.2 (34.8)	6
PAA	65.3 (46.3)	9.24, 242	69	6.08 (0.583, 8.08)	69	2064 (1322)	379, 6811	60	11.4 (7.08)	60	NC	0	NC	0	NC	0
PAGN	74.9 (19.5)	32.8, 126	69	6.08 (2.58, 8.12)	69	1642 (429)	902, 2837	68	20.8 (5.54)	68	NC	0	NC	0	NC	0
<b>Treatment E</b> (9 mL HPN-100 TID):																
PBA	147 (56.5)	97.6, 243	5	3.08 (3.08, 6.08)	5	1745 (372)	1352, 2154	5	17.7 (3.73)	5	NC	1	NC	1	NC	1
PAA	149 (107)	65.0, 328	5	6.08 (2.13, 6.10)	5	3684 (1722)	2045, 6464	5	7.77 (3.10)	5	NC	0	NC	0	NC	0
PAGN	115 (26.1)	80.4, 138	5	6.08 (4.08, 6.08)	5	2298 (331)	1865, 2715	5	21.2 (3.16)	5	NC	0	NC	0	NC	0

<sup>a</sup>  $C_{max}$  was calculated for the first dose on Day 3.

<sup>b</sup> Median (Min, Max) presented for  $T_{max}$ .

Note: Treatment C = 13.2 g/day (4 mL TID) HPN-100. Treatment D = 19.8 g/day (6 mL TID) HPN-100. Treatment E = 29.7 g/day (9 mL TID) HPN-100.

NC = Not calculated.

Note:  $T_{max}$  and  $C_{max}$  shown in the sponsor's table above correspond to the peak concentrations of metabolites after the first dose of the day, (essentially before the second dose of the day, thus it does not represent the true daily max concentration).

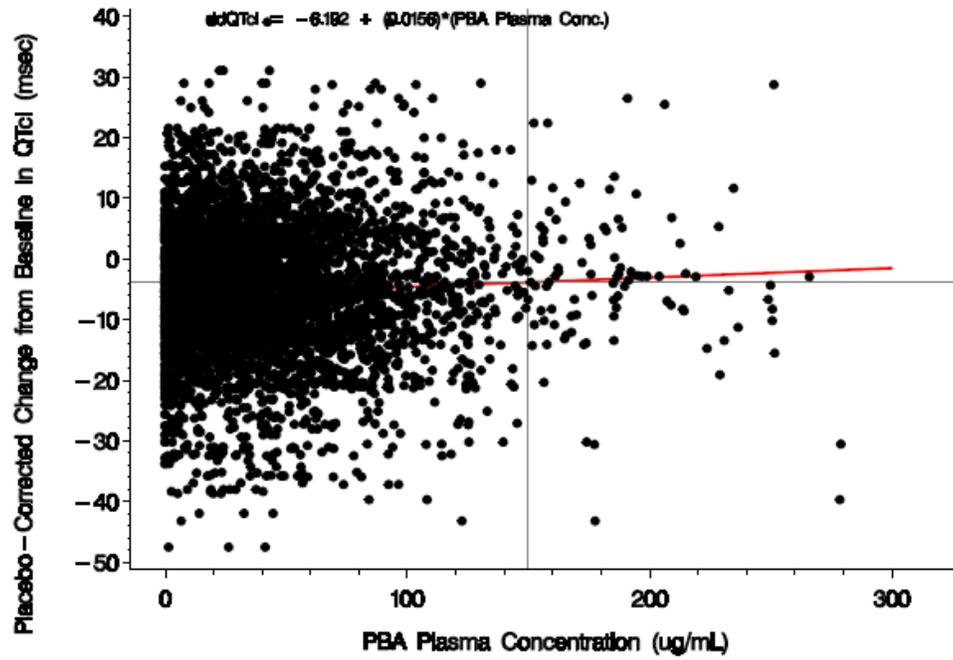
*Source: Table 11-6 of sponsor's study report*

#### **4.2.8.4.2 Exposure-Response Analysis**

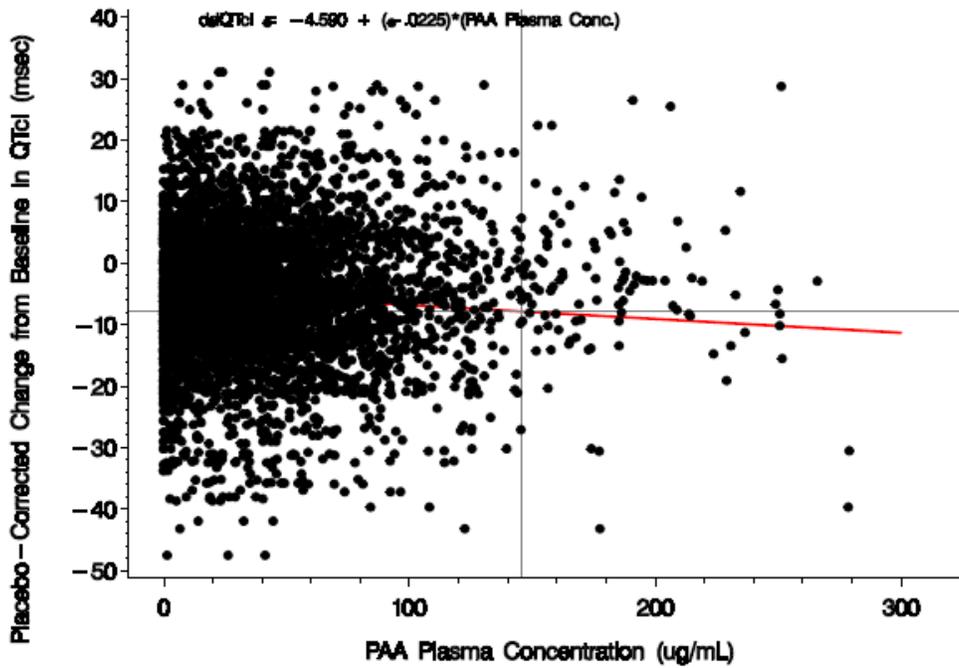
Sponsor's  $\Delta\Delta Q_{TcI}$  vs. HPN-100 metabolite (PBA, PAA, PAGN) plasma concentrations are shown in Figure 2.

Figure 2: Sponsor's Concentration- $\Delta\Delta$ QTcI relationship for HPN-100 metabolites: A) PBA, B) PAA, and C) PAGN

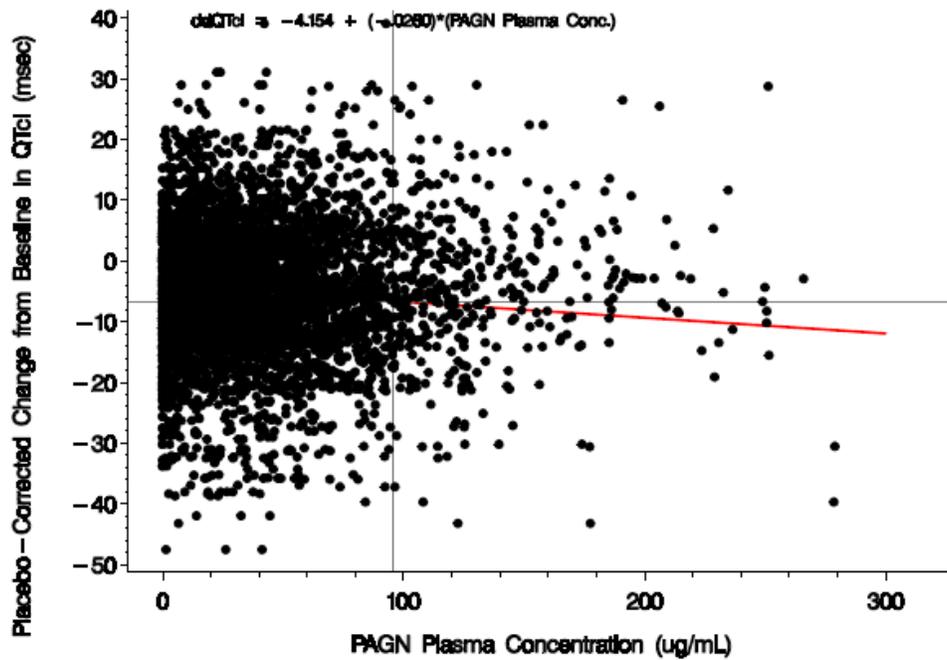
A)



B)



C)



Source: Figure 11-11, 11-12 and 11-13 in sponsor's study report

Reviewer's Comments: A plot of  $\Delta\Delta QTcI$  vs. PBA (HPN-100 metabolite) concentration is presented in Figure 5. A slight trend for increase in  $QTcI$  prolongation is observed with increasing PBA concentration. This increase is not clinically meaningful within the concentration range seen in patients.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

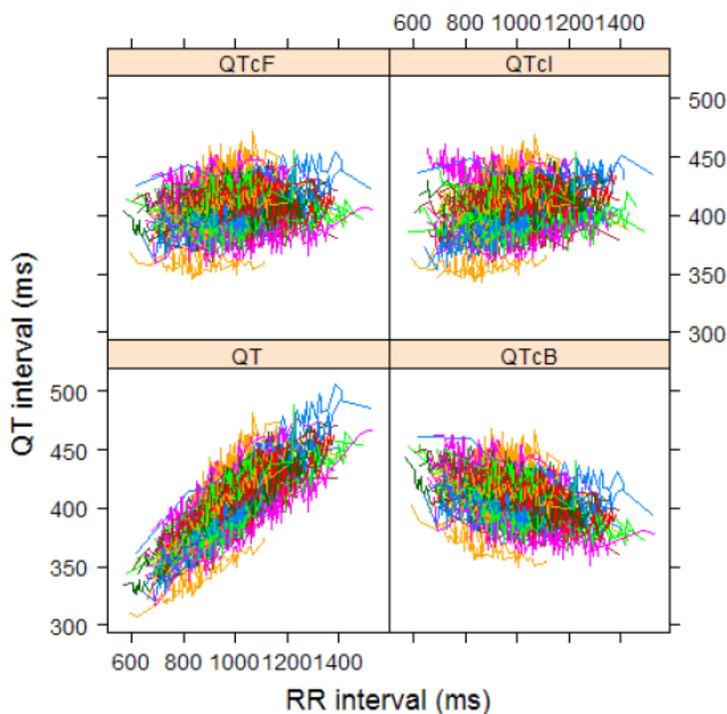
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it also appears that QTcF and QTcI are similar in RR correction. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

**Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment									
	HPN-100 13.2 g/day		HPN-100 19.8 g/day		Moxifloxaci n 400 mg		Placebo		All	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	66	0.0052	62	0.0083	70	0.0041	72	0.0052	79	0.0053
QTcF	66	0.0012	62	0.0023	70	0.0018	72	0.0015	79	0.0016
QTcI	64	0.0015	58	0.0022	69	0.0021	70	0.0012	71	0.0016

The relationship between different correction methods and RR is presented in Figure 3.

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for HPN-100

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model includes time point, sequence and period as fixed effects and subject as a random effect.

Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 6: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group = HPN-100 13.2 g/day**

	HPN-100 13.2 g/day $\Delta$ QTcI	Placebo $\Delta$ QTcI	$\Delta\Delta$ QTcI	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-8.5	-4.4	-4.2	(-6.3, -2.1)
1	-9.5	-6.2	-3.3	(-5.3, -1.3)
1.5	-9.8	-7.0	-2.8	(-5.0, -0.7)
2	-11.5	-8.2	-3.3	(-5.2, -1.3)
2.5	-12.0	-7.5	-4.5	(-6.5, -2.5)
3	-11.7	-5.7	-6.0	(-8.2, -3.7)
4	-9.8	-4.2	-5.6	(-7.6, -3.6)
6	-12.1	-8.5	-3.6	(-5.5, -1.7)
8	-15.8	-10.8	-5.0	(-7.1, -2.9)
12	-14.6	-11.8	-2.8	(-4.8, -0.8)
16	-9.8	-2.9	-6.9	(-9.4, -4.3)
23	-6.9	-2.1	-4.8	(-6.9, -2.7)

**Table 7: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group = HPN-100 19.8 g/day**

	HPN-100 19.8 g/day $\Delta$ QTcI	Placebo $\Delta$ QTcI	$\Delta\Delta$ QTcI	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-9.9	-4.4	-5.5	(-7.7, -3.4)
1	-11.4	-6.2	-5.2	(-7.2, -3.1)
1.5	-11.1	-7.0	-4.1	(-6.3, -2.0)
2	-12.7	-8.2	-4.4	(-6.4, -2.4)
2.5	-13.3	-7.5	-5.8	(-7.9, -3.7)
3	-12.9	-5.7	-7.2	(-9.5, -4.9)
4	-10.8	-4.2	-6.6	(-8.6, -4.6)
6	-13.7	-8.5	-5.2	(-7.1, -3.2)
8	-15.0	-10.8	-4.2	(-6.4, -2.1)
12	-15.2	-11.8	-3.4	(-5.5, -1.3)
16	-10.9	-2.9	-7.9	(-10.6, -5.3)
23	-8.9	-2.1	-6.7	(-8.9, -4.6)

The largest upper bounds of the 2-sided 90% CI for the mean difference between HPN-100 13.2 g/day and placebo, and between HPN-100 19.8 g/day and placebo were -0.7 ms and -1.3 ms, respectively.

#### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 7.0 ms after considering Bonferroni multiple endpoint adjustment, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin**

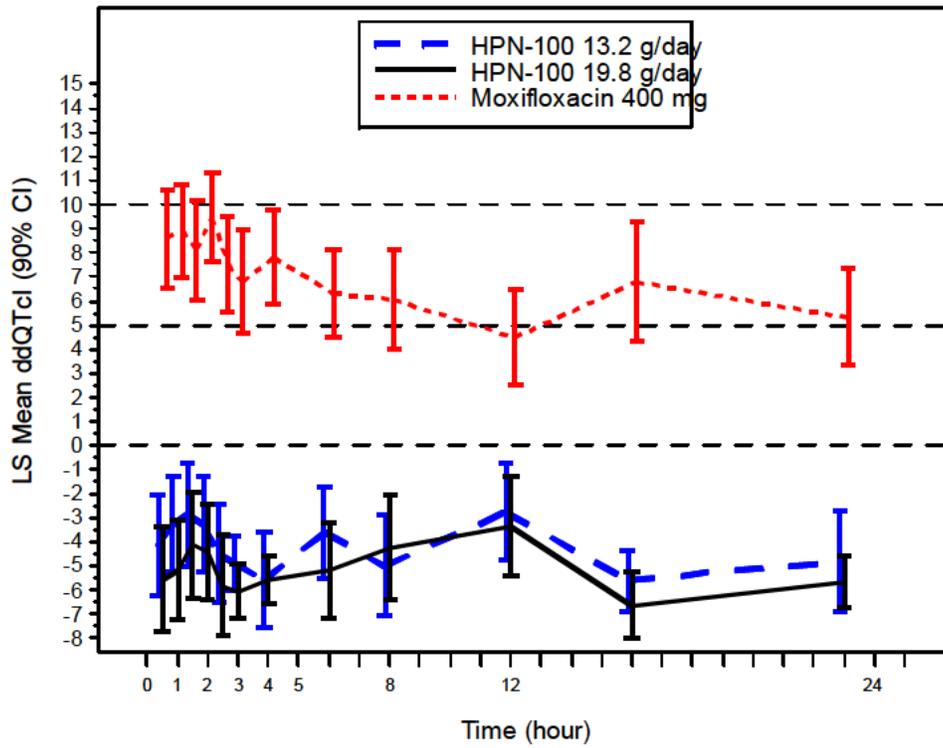
	Moxifloxacin 400 mg	Placebo $\Delta$ QTcI	$\Delta\Delta$ QTcI	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	4.2	-4.4	8.6	(5.9, 11.2)
1	2.7	-6.2	8.9	(6.4, 11.4)
1.5	1.2	-7.0	8.1	(5.4, 10.8)
2	1.2	-8.2	9.5	(7.0, 11.9)
2.5	0.0	-7.5	7.5	(5.0, 10.1)
3	1.0	-5.7	6.8	(4.0, 9.6)
4	3.6	-4.2	7.8	(5.3, 10.3)
6	-2.2	-8.5	6.3	(3.9, 8.7)
8	-4.8	-10.8	6.0	(3.4, 8.7)
12	-7.4	-11.8	4.5	(1.9, 7.0)
16	3.8	-2.9	6.8	(3.5, 10.0)
23	3.2	-2.1	5.3	(2.7, 7.9)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups.

Figure 4: Mean and 90% CI  $\Delta\Delta$ QTcI Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 9: Categorical Analysis for QTcI**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
HPN-100 13.2 g/day	64	760	63 (98.4%)	759 (99.9%)	1 (1.6%)	1 (0.1%)
HPN-100 19.8 g/day	58	690	56 (96.6%)	683 (99.0%)	2 (3.4%)	7 (1.0%)
Moxifloxacin 400 mg	69	826	63 (91.3%)	805 (97.5%)	6 (8.7%)	21 (2.5%)
Placebo	70	834	69 (98.6%)	831 (99.6%)	1 (1.4%)	3 (0.4%)

Table 10 lists the categorical analysis results for  $\Delta$ QTcI. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
HPN-100 13.2 g/day	64	760	64 (100%)	760 (100%)	0 (0.0%)	0 (0.0%)
HPN-100 19.8 g/day	58	690	58 (100%)	690 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	69	826	67 (97.1%)	824 (99.8%)	2 (2.9%)	2 (0.2%)
Placebo	70	834	69 (98.6%)	833 (99.9%)	1 (1.4%)	1 (0.1%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11 and Table 12. The largest upper limits of 90% CI for the HR mean differences between HPN-100 13.2 g/day and placebo, and between HPN-100 19.8 g/day and placebo were -0.7 bpm and -1.3 bpm, respectively.

**Table 11: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = HPN-100 13.2 g/day**

Time (h)	HPN-100 13.2 g/day $\Delta$ HR	Placebo $\Delta$ HR	$\Delta\Delta$ HR	
	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	4.6	5.8	-1.2	(-2.7, 0.3)
1	6.6	6.6	0.1	(-1.4, 1.5)
1.5	6.7	6.8	-0.2	(-1.7, 1.3)
2	5.9	5.6	0.3	(-1.2, 1.8)
2.5	5.3	3.7	1.6	(0.2, 3.1)
3	3.5	2.9	0.6	(-0.7, 2.0)
4	3.7	1.8	1.9	(0.2, 3.5)
6	11.0	10.9	0.1	(-1.4, 1.6)
8	9.0	5.3	3.7	(2.0, 5.4)
12	14.0	9.4	4.6	(3.0, 6.1)
16	8.1	4.6	3.5	(1.8, 5.1)
23	2.8	3.7	-1.0	(-2.7, 0.8)

**Table 12: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = HPN-100 19.8 g/day**

	<b>HPN-100 19.8/day <math>\Delta</math>HR</b>	<b>Placebo <math>\Delta</math>HR</b>	<b><math>\Delta\Delta</math>HR</b>	
<b>Time (h)</b>	<b>LS Mean (bpm)</b>	<b>LS Mean (bpm)</b>	<b>Diff LS Mean (bpm)</b>	<b>90% CI (bpm)</b>
0.5	8.3	5.8	2.5	(1.0, 4.1)
1	8.4	6.6	1.8	(0.3, 3.3)
1.5	8.7	6.8	1.9	(0.4, 3.4)
2	9.0	5.6	3.4	(1.9, 5.0)
2.5	7.8	3.7	4.2	(2.7, 5.6)
3	7.6	2.9	4.7	(3.3, 6.1)
4	7.5	1.8	5.7	(4.0, 7.4)
6	16.8	10.9	5.9	(4.3, 7.4)
8	13.6	5.3	8.3	(6.6, 10.0)
12	19.9	9.4	10.5	(8.9, 12.1)
16	15.4	4.6	10.8	(9.1, 12.6)
23	6.0	3.7	2.3	(0.5, 4.1)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the PR mean differences between HPN-100 13.2 g/day and placebo, and between HPN-100 19.8 g/day and placebo were 4.9 ms and 4.2 ms, respectively.

**Table 13: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = HPN-100 13.2 g/day**

	HPN-100 13.2 g/day $\Delta$ PR	Placebo $\Delta$ PR	$\Delta\Delta$ PR	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.6	-0.4	1.0	(-1.1, 3.1)
1	1.6	-0.5	2.2	(0.0, 4.3)
1.5	0.4	-1.3	1.7	(-0.3, 3.7)
2	-0.5	-2.8	2.3	(0.3, 4.2)
2.5	-1.5	-4.5	2.9	(1.0, 4.9)
3	-2.6	-4.1	1.5	(-0.4, 3.4)
4	-2.7	-5.7	2.9	(1.0, 4.9)
6	-5.4	-6.5	1.1	(-0.9, 3.0)
8	-7.4	-7.2	-0.2	(-2.1, 1.7)
12	-8.1	-8.1	0.0	(-2.0, 2.1)
16	-4.4	-3.6	-0.8	(-2.8, 1.2)
23	-0.8	-2.9	2.1	(0.2, 4.1)

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = HPN-100 19.8 g/day**

	<b>HPN-100 19.8 g/day <math>\Delta</math>PR</b>	<b>Placebo <math>\Delta</math>PR</b>	<b><math>\Delta\Delta</math>PR</b>	
<b>Time (h)</b>	<b>LS Mean (ms)</b>	<b>LS Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
0.5	-0.3	-0.4	0.1	(-2.0, 2.3)
1	-0.1	-0.5	0.4	(-1.8, 2.6)
1.5	-1.7	-1.3	-0.4	(-2.5, 1.6)
2	-2.9	-2.8	-0.1	(-2.1, 1.9)
2.5	-2.3	-4.5	2.2	(0.2, 4.2)
3	-3.7	-4.1	0.4	(-1.6, 2.3)
4	-4.5	-5.7	1.2	(-0.8, 3.2)
6	-6.9	-6.5	-0.4	(-2.5, 1.6)
8	-7.7	-7.2	-0.4	(-2.4, 1.5)
12	-8.7	-8.1	-0.6	(-2.7, 1.5)
16	-4.8	-3.6	-1.2	(-3.4, 0.9)
23	-3.0	-2.9	-0.1	(-2.1, 1.9)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest upper limits of 90% CI for the QRS mean differences between PN-100 13.2 g/day and placebo, and between HPN-100 19.8 g/day and placebo were 1.0 ms and 1.5 ms, respectively.

**Table 15: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = HPN-100 13.2 g/day**

	HPN-100 13.2 g/day $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.5	0.4	-1.0	(-1.8, -0.1)
1	-0.4	0.0	-0.4	(-1.3, 0.4)
1.5	-0.5	0.0	-0.5	(-1.4, 0.3)
2	-0.5	-0.4	-0.1	(-0.9, 0.7)
2.5	-0.9	-0.4	-0.5	(-1.3, 0.3)
3	-0.9	-0.9	0.0	(-0.7, 0.8)
4	-1.3	-1.2	-0.1	(-0.8, 0.6)
6	-0.7	-0.2	-0.5	(-1.2, 0.3)
8	-1.6	-1.7	0.1	(-0.7, 0.8)
12	-2.0	-1.4	-0.6	(-1.4, 0.1)
16	-0.5	-0.6	0.1	(-0.7, 1.0)
23	-0.5	-0.6	0.1	(-0.7, 0.9)

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = HPN-100 19.8 g/day**

	HPN-100 13.2 g/day $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.7	0.4	0.2	(-0.7, 1.1)
1	0.5	0.0	0.5	(-0.4, 1.4)
1.5	0.2	0.0	0.2	(-0.7, 1.1)
2	-0.3	-0.4	0.2	(-0.7, 1.0)
2.5	-0.3	-0.4	0.1	(-0.7, 0.9)
3	-0.3	-0.9	0.7	(-0.1, 1.5)
4	-0.9	-1.2	0.3	(-0.4, 1.0)
6	-0.6	-0.2	-0.4	(-1.2, 0.4)
8	-1.5	-1.7	0.2	(-0.6, 0.9)
12	-2.4	-1.4	-1.0	(-1.8, -0.2)
16	-0.8	-0.6	-0.2	(-1.1, 0.6)
23	-0.1	-0.6	0.5	(-0.3, 1.4)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta\Delta$ QTcI and HPN-100 metabolites (PBA, PAA and PAGN) concentrations was investigated by linear mixed-effects modeling. Amongst three different models, a linear model with intercept was used for further analysis since this model was found to fit the data best.

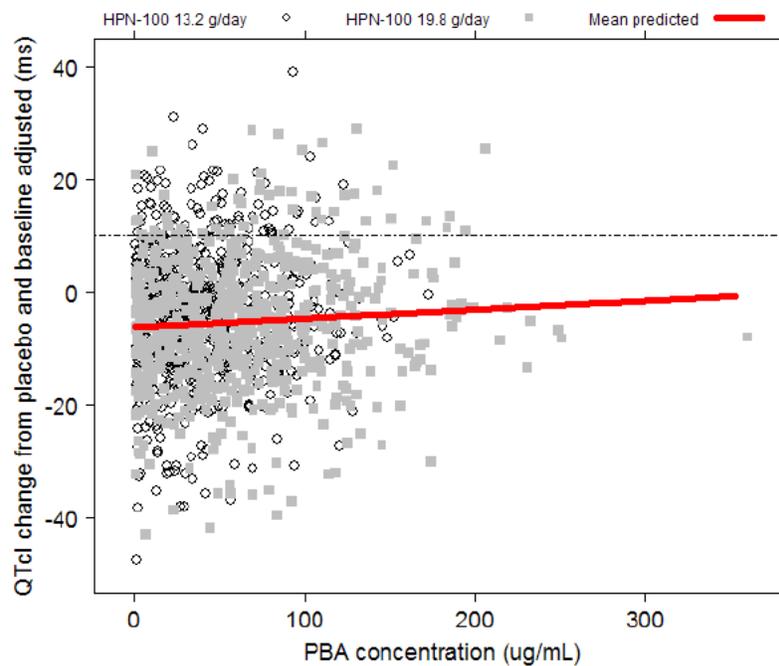
Table 17 summarizes the results of the PBA concentration- $\Delta\Delta$ QTcI analyses. The exposure-response relationship between  $\Delta\Delta$ QTcI and PBA (HPN-100 metabolite) concentration is visualized in Figure 5. There is a modest increase in QTcI prolongation with increase in PBA concentration. This increase is not clinically meaningful within the concentration range seen in patients. Also, the relationships between  $\Delta\Delta$ QTcI and other HPN-100 metabolites (PAA and PAGN) concentration was explored (not shown here), with no apparent exposure-response relationship for these metabolites. The goodness-of-fit plot in Figure 6 shows the observed median-quantile PBA concentrations and associated mean (90% CI)  $\Delta\Delta$ QTcI together with the mean (90% CI) predicted  $\Delta\Delta$ QTcI. The mean (90% CI) predicted  $\Delta\Delta$ QTcI at the mean peak PBA concentrations for

therapeutic and suprathreshold HPN-100 doses is below 0 ms as shown in Figure 7 and thus are not clinically relevant.

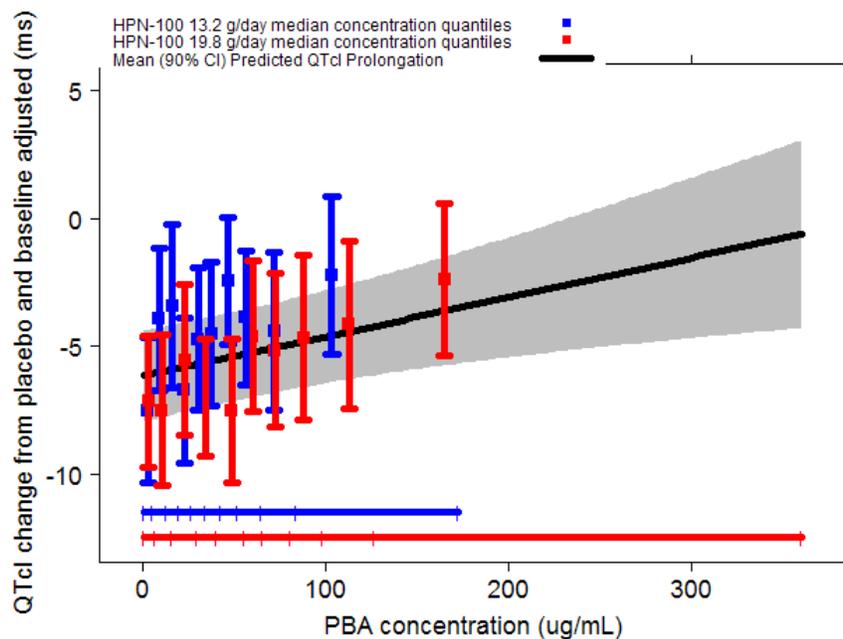
**Table 17: Exposure-Response Analysis of PBA Associated with  $\Delta\Delta\text{QTcI}$**

Parameter	Estimate	P-value
$\Delta\Delta\text{QTcI} = \text{Intercept} + \text{slope} * \text{PBA Concentration}$		
Intercept (ms)	-6.17 (-7.96; -4.38)	<0.0001
Slope (ms per $\mu\text{g/mL}$ )	0.0154 (0.00506; 0.0258)	0.017
Residual Variability (ms)	8.08	

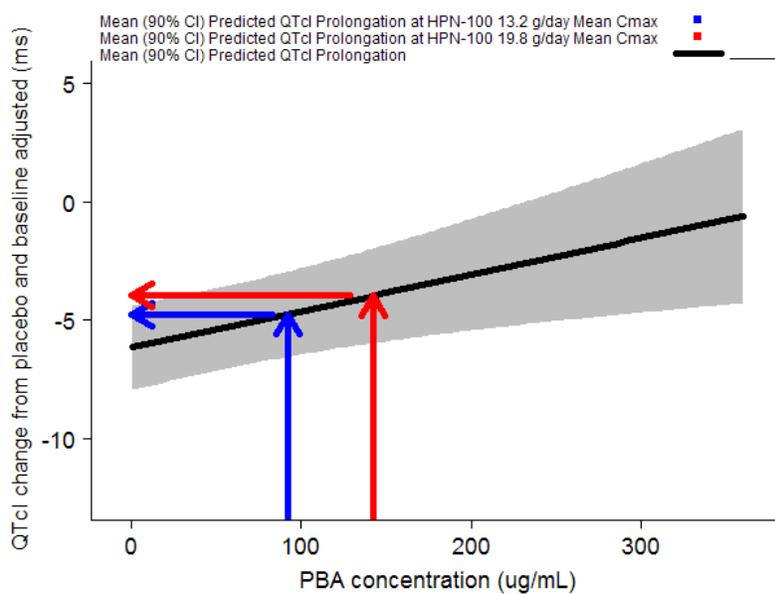
**Figure 5:  $\Delta\Delta\text{QTcI}$  vs. PBA (HPN-100 metabolite) concentration**



**Figure 6: Observed Median-Quantile PBA Concentration and Associated Mean (90% CI)  $\Delta\Delta$ QTcI (colored dots) together with the Mean (90% CI) Predicted  $\Delta\Delta$ QTcI (black line with shaded grey area)**



**Figure 7: Mean (90% CI) Predicted  $\Delta\Delta$ QTcI at Mean  $C_{max}$  for PBA**



## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 98% of the ECGs were annotated in the primary lead II, with less than 0.05% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

Four subjects had PR >200 ms. No post-baseline PR values were >210 ms. One subject experienced a post-baseline QRS of 114 ms. None of these findings were clinically relevant.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Include maximum proposed clinical dosing regimen. 4.4 g TID (4 mL TID); 13.4 g/day total (12 mL/day total) was the therapeutic dose in the QTc study ( <a href="#">protocol HPN-100-010</a> )																	
Maximum tolerated dose	Include if studied or NOAEL dose 6.6 g TID (6 mL TID); 19.8 g/day total (18 mL/day total) was the supratherapeutic dose in the QTc study ( <a href="#">protocol HPN-100-010</a> )																	
Principal adverse events	Include most common adverse events; dose limiting adverse events headache, nausea, dizziness, and vomiting																	
Maximum dose tested	Single Dose	Specify dose 13.2 g (12 mL)																
	Multiple Dose	Specify dosing interval and duration 13.2 g TID (12 mL TID); 39.6 g/day total (36 mL/day total).																
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) and AUC<sub>0-24</sub> (µg·h/mL)</p> <p>CV% not calculated in the Clinical study Report (CSR). Values given are mean (SD)</p> <p>AUC<sub>0-8</sub> is provided since the 2<sup>nd</sup> dose was administered at 8 hours and AUC<sub>0-24</sub> were not applicable</p> <table border="1"> <thead> <tr> <th>Metabolite (N)</th> <th>Cmax (µg/mL)</th> <th>AUC<sub>0-8</sub> (µg·h/mL)</th> </tr> </thead> <tbody> <tr> <td>PBA (4)</td> <td>184 (83.5)</td> <td>589 (350)</td> </tr> <tr> <td>PAA (4)</td> <td>68.2 (23.0)</td> <td>363 (147)</td> </tr> <tr> <td>PAGN (4)</td> <td>66.7 (11.7)</td> <td>371 (73.2)</td> </tr> </tbody> </table>		Metabolite (N)	Cmax (µg/mL)	AUC <sub>0-8</sub> (µg·h/mL)	PBA (4)	184 (83.5)	589 (350)	PAA (4)	68.2 (23.0)	363 (147)	PAGN (4)	66.7 (11.7)	371 (73.2)			
	Metabolite (N)	Cmax (µg/mL)	AUC <sub>0-8</sub> (µg·h/mL)															
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PAGN (4)	66.7 (11.7)	371 (73.2)																
Multiple Dose	<p>Mean (%CV) Cmax (µg/mL) and AUC<sub>0-24</sub> (µg·h/mL)</p> <p>Range (Min, Max) is provided for multiple dose due to N = 2 and mean,SD, %CV could not be calculated</p> <table border="1"> <thead> <tr> <th>Metabolite (N)</th> <th>Cmax (µg/mL)</th> <th>AUC<sub>0-8</sub> (µg·h/mL)</th> <th>AUC<sub>0-24</sub> (µg·h/mL)</th> </tr> </thead> <tbody> <tr> <td>PBA (2)</td> <td>(207, 222)</td> <td>(633, 771)</td> <td>(1165, 1495)</td> </tr> <tr> <td>PAA (2)</td> <td>(328, 435)</td> <td>(2123, 3167)</td> <td>(8227, 9694)</td> </tr> <tr> <td>PAGN (2)</td> <td>(153, 170)</td> <td>(1149, 1186)</td> <td>(3516, 3684)</td> </tr> </tbody> </table> <p>AUC<sub>0-8</sub> is also provided for comparison with single dose exposure</p>		Metabolite (N)	Cmax (µg/mL)	AUC <sub>0-8</sub> (µg·h/mL)	AUC <sub>0-24</sub> (µg·h/mL)	PBA (2)	(207, 222)	(633, 771)	(1165, 1495)	PAA (2)	(328, 435)	(2123, 3167)	(8227, 9694)	PAGN (2)	(153, 170)	(1149, 1186)	(3516, 3684)
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PAGN (2)	(153, 170)	(1149, 1186)	(3516, 3684)															

Range of linear PK	<p>Specify dosing regimen</p> <p>Linear PK behavior was observed across 4, 6 and 9 mL TID dosing (13.2 g/day, 19.8 g/day and 29.7 g/day). Due to limited number of subjects in the 12 mL TID dose (39.6 g/day), linearity cannot be assessed.</p> <p>From CSR page 98: Comparing 4 mL TID with 6 mL TID the mean <math>C_{max}</math> increased approximately 51%, 132%, and 60%, for PBA, PAA, and PAGN, and the mean <math>AUC_{0-23}</math> increased approximately 50%, 119%, and 74% for PBA, PAA, and PAGN, respectively.</p> <p>Comparing 6 mL TID and 9 mL TID (a 50% increase in dose), the mean <math>C_{max}</math> increased 47%, 128%, and 54% for PBA, PAA, and PAGN, respectively and the mean <math>AUC_{0-23}</math> values increased approximately 25%, 78% and 40%, for PBA, PAA, and PAGN, respectively.</p>																													
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen</p> <p>CV% of accumulation ratio was not reported in CSR.</p> <table border="1" data-bbox="570 701 1328 890"> <thead> <tr> <th rowspan="3">Metabolite</th> <th colspan="4">Accumulation Ratio</th> </tr> <tr> <th colspan="2"><math>C_{max}</math></th> <th colspan="2"><math>AUC_{0-8}</math></th> </tr> <tr> <th>9 mL TID</th> <th>12 mL TID</th> <th>9 mL TID</th> <th>12 mL TID</th> </tr> </thead> <tbody> <tr> <td>PBA</td> <td>2.7</td> <td>1.1 to 1.2</td> <td>2.9</td> <td>1.1 to 1.3</td> </tr> <tr> <td>PAA</td> <td>11.1</td> <td>4.8 to 6.4</td> <td>15.8</td> <td>5.8 to 8.7</td> </tr> <tr> <td>PAGN</td> <td>2.8</td> <td>2.3 to 2.5</td> <td>3.7</td> <td>3.1 to 3.2</td> </tr> </tbody> </table> <p>Range (Min, Max) is provided for multiple dose for 12 mL TID due to N = 2 and mean could not be calculated</p>		Metabolite	Accumulation Ratio				$C_{max}$		$AUC_{0-8}$		9 mL TID	12 mL TID	9 mL TID	12 mL TID	PBA	2.7	1.1 to 1.2	2.9	1.1 to 1.3	PAA	11.1	4.8 to 6.4	15.8	5.8 to 8.7	PAGN	2.8	2.3 to 2.5	3.7	3.1 to 3.2
Metabolite	Accumulation Ratio																													
	$C_{max}$			$AUC_{0-8}$																										
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PAGN	2.8	2.3 to 2.5	3.7	3.1 to 3.2																										
Metabolites	<p>Include listing of all metabolites and activity</p> <p>PBA, PAA (active metabolite), PAGN (terminal metabolite)</p>																													
Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV)</p> <p>Not calculated</p> <p>Tmax</p> <ul style="list-style-type: none"> <li>• Median (range) for parent: NA, parent (intact HPN-100) not measureable in plasma</li> </ul> <p>Median (range) Tmax</p> <table border="1" data-bbox="813 1268 1333 1488"> <thead> <tr> <th rowspan="2">Metabolite</th> <th colspan="3"><math>T_{max}</math> (hr)</th> </tr> <tr> <th>4 mL TID</th> <th>6 mL TID</th> <th>9 mL TID</th> </tr> </thead> <tbody> <tr> <td>PBA</td> <td>2.58 (1.08, 6.22)</td> <td>6.08 (1.12, 8.00)</td> <td>3.08 (3.08, 6.08)</td> </tr> <tr> <td>PAA</td> <td>4.08 (2.08, 6.13)</td> <td>6.08 (0.58, 8.08)</td> <td>6.08 (2.13, 6.10)</td> </tr> <tr> <td>PAGN</td> <td>4.08 (2.08, 6.13)</td> <td>6.08 (2.58, 8.12)</td> <td>6.08 (4.08, 6.08)</td> </tr> </tbody> </table>	Metabolite	$T_{max}$ (hr)			4 mL TID	6 mL TID	9 mL TID	PBA	2.58 (1.08, 6.22)	6.08 (1.12, 8.00)	3.08 (3.08, 6.08)	PAA	4.08 (2.08, 6.13)	6.08 (0.58, 8.08)	6.08 (2.13, 6.10)	PAGN	4.08 (2.08, 6.13)	6.08 (2.58, 8.12)	6.08 (4.08, 6.08)									
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PAGN	4.08 (2.08, 6.13)	6.08 (2.58, 8.12)	6.08 (4.08, 6.08)																											

Distribution	Vd/F or Vd	<p>Mean (%CV):</p> <p>Vd/F or Vd not calculated. Values calculated were <b>V<sub>z</sub>/F or V<sub>z</sub>/F<sub>m</sub></b>.</p> <p>CV% not calculated. Values are mean (SD)</p> <table border="1"> <thead> <tr> <th rowspan="2">Metabolite</th> <th colspan="3">V<sub>z</sub>/F or V<sub>z</sub>/F<sub>m</sub> (L)</th> </tr> <tr> <th>4 mL TID</th> <th>6 mL TID</th> <th>9 mL TID</th> </tr> </thead> <tbody> <tr> <td>PBA</td> <td>96.9 (73.5)</td> <td>77.2 (34.8)</td> <td>NC</td> </tr> <tr> <td>PAA</td> <td>NC</td> <td>NC</td> <td>NC</td> </tr> <tr> <td>PAGN</td> <td>NC</td> <td>NC</td> <td>NC</td> </tr> </tbody> </table> <p>NC= Not calculable.</p>	Metabolite	V <sub>z</sub> /F or V <sub>z</sub> /F <sub>m</sub> (L)			4 mL TID	6 mL TID	9 mL TID	PBA	96.9 (73.5)	77.2 (34.8)	NC	PAA	NC	NC	NC	PAGN	NC	NC	NC
	Metabolite	V <sub>z</sub> /F or V <sub>z</sub> /F <sub>m</sub> (L)																			
4 mL TID		6 mL TID	9 mL TID																		
PBA	96.9 (73.5)	77.2 (34.8)	NC																		
PAA	NC	NC	NC																		
PAGN	NC	NC	NC																		
% bound	Mean (%CV)	Not assessed in HPN-100-010 study																			
Elimination	Route	<ul style="list-style-type: none"> <li>Primary route; percent dose eliminated: Following oral administration, approximately 60%, 49%, and 35% of the dose was recovered in urine in 24 hours as PAGN with 4 mL TID (n = 66), 6 mL TID (n = 69), and 9 mL TID (n = 5)</li> <li>Other routes: NA</li> </ul>																			
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>Mean (%CV) for parent: NA, parent (intact HPN-100) not measureable in plasma</li> <li>CV% not calculated in the CSR. Values given are mean (SD)</li> </ul> <p>Mean (SD) for metabolites: 4 mL; 6 mL; 9 mL TID</p> <p>PBA: 3.88 (2.77); 3.85 (2.65); Not calculable</p> <p>PAA: Not calculable</p> <p>PAGN: Not calculable</p>																			
	CL/F or CL	<p>Mean (%CV)</p> <p>CV% not calculated in the CSR. Values given are mean (SD)</p> <table border="1"> <thead> <tr> <th rowspan="2">Metabolite</th> <th colspan="3">CL/F or CL/F<sub>m</sub> (L/hr)</th> </tr> <tr> <th>4 mL TID</th> <th>6 mL TID</th> <th>9 mL TID</th> </tr> </thead> <tbody> <tr> <td>PBA</td> <td>15.0 (3.63)</td> <td>16.2 (6.79)</td> <td>17.7 (3.73)</td> </tr> <tr> <td>PAA</td> <td>14 (8.84)</td> <td>11.4 (7.08)</td> <td>7.77 (3.10)</td> </tr> <tr> <td>PAGN</td> <td>23.8 (6.27)</td> <td>20.8 (5.54)</td> <td>21.2 (3.16)</td> </tr> </tbody> </table>	Metabolite	CL/F or CL/F <sub>m</sub> (L/hr)			4 mL TID	6 mL TID	9 mL TID	PBA	15.0 (3.63)	16.2 (6.79)	17.7 (3.73)	PAA	14 (8.84)	11.4 (7.08)	7.77 (3.10)	PAGN	23.8 (6.27)	20.8 (5.54)	21.2 (3.16)
Metabolite	CL/F or CL/F <sub>m</sub> (L/hr)																				
	4 mL TID	6 mL TID	9 mL TID																		
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PAGN	23.8 (6.27)	20.8 (5.54)	21.2 (3.16)																		

Intrinsic Factors	Age	Specify mean changes in Cmax and AUC All patients in <a href="#">protocol HPN-100-010</a> were adults
	Sex	Specify mean changes in Cmax and AUC Analysis was dose normalized (DN) Cmax and DN AUC (DNAUC <sub>0-23</sub> ) PBA: 4mL TID: mean DNC <sub>max</sub> was ~ 24% higher for women; mean DNAUC <sub>0-23</sub> for PBA did not differ significantly. 6 mL TID: 36% higher in women PAA: 4 mL TID: mean DNC <sub>max</sub> was ~51% higher in women. 6 mL TID: ~120% higher in women. The mean DNAUC <sub>0-23</sub> for PAA was approximately 108% higher in women (treatments combined). PAGN: the mean DNC <sub>max</sub> was approximately 17% higher in women in the 6 mL TID group only. The mean DNAUC <sub>0-23</sub> for PAGN was approximately 21% higher for women in the 6 mL TID group only. DN PAGN excreted in the urine in women was approximately 14% lower in women than men
	Race	Specify mean changes in Cmax and AUC Effects of race were not assessed in <a href="#">HPN-100-010</a> study
	Hepatic & Renal Impairment	Specify mean changes in Cmax (µg/mL) and AUC (AUC <sub>0-12</sub> µg·h/mL) All study subjects were healthy adults. No hepatic or renal impaired patients were included in the study
	Extrinsic Factors	Drug interactions
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) Effects of food were not assessed in <a href="#">HPN-100-010</a> study

Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>The supra-therapeutic dose tested in HPN-100-010 study was 6 mL TID (18 mL total/day or 19.8 g/day). The proposed maximum labeled dose of HPN-100 is (b) (4) mL/day or (b) (4) g/day. Below is the range of exposures (min, max) reported in UCD patients and HPN-100-010</p> <table border="1" data-bbox="565 401 1187 709"> <thead> <tr> <th></th> <th colspan="2">QTe study</th> <th colspan="2">UCD</th> </tr> <tr> <th></th> <th>18+</th> <th>18+</th> <th colspan="2">6-17 yr</th> </tr> </thead> <tbody> <tr> <td><b>Dose range g/day</b></td> <td><b>19.8</b></td> <td><b>1.7, 34.3</b></td> <td colspan="2"><b>8.3, 19.1</b></td> </tr> <tr> <td><b>AUC<sub>0-24 hr</sub></b></td> <td colspan="4">Minimum, Maximum</td> </tr> <tr> <td>PBA</td> <td>570, 2074</td> <td>16.2, 1497</td> <td colspan="2">248, 1244</td> </tr> <tr> <td>PAA</td> <td>379, 6811</td> <td>9.54, 3139</td> <td colspan="2">129, 2317</td> </tr> <tr> <td>PAGN</td> <td>902, 2837</td> <td>151, 2979</td> <td colspan="2">576, 2337</td> </tr> <tr> <td><b>C<sub>max</sub></b></td> <td colspan="4"></td> </tr> <tr> <td>PBA</td> <td>27.0, 187</td> <td>2.22, 145</td> <td colspan="2">27.4, 161</td> </tr> <tr> <td>PAA</td> <td>9.24, 242</td> <td>1.60, 178</td> <td colspan="2">17.8, 244</td> </tr> <tr> <td>PAGN</td> <td>32.8, 126</td> <td>11.1, 183</td> <td colspan="2">44.5, 153</td> </tr> </tbody> </table>		QTe study		UCD			18+	18+	6-17 yr		<b>Dose range g/day</b>	<b>19.8</b>	<b>1.7, 34.3</b>	<b>8.3, 19.1</b>		<b>AUC<sub>0-24 hr</sub></b>	Minimum, Maximum				PBA	570, 2074	16.2, 1497	248, 1244		PAA	379, 6811	9.54, 3139	129, 2317		PAGN	902, 2837	151, 2979	576, 2337		<b>C<sub>max</sub></b>					PBA	27.0, 187	2.22, 145	27.4, 161		PAA	9.24, 242	1.60, 178	17.8, 244		PAGN	32.8, 126	11.1, 183	44.5, 153	
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOANNE ZHANG  
05/30/2012

QIANYU DANG  
05/30/2012

DHANANJAY D MARATHE  
05/30/2012

NITIN MEHROTRA  
05/30/2012

MONICA L FISZMAN  
05/31/2012

NORMAN L STOCKBRIDGE  
05/31/2012

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 203284

**Name of Drug:** Ravicti (glycerol phenylbutyrate) liquid

**Applicant:** Ucyclud Pharma (US Agent: Hyperion Therapeutics)

## **Labeling Reviewed**

**Submission Date:** 12/23/2011

**Receipt Date:** 12/23/2011

## **Background and Summary Description**

Ravicti (glycerol phenylbutyrate) liquid is a new molecular entity that provides for adjunctive therapy for chronic management of adults and children (6-17 years of age) with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH deficiency). Ravicti was granted orphan designation and fast track designation on 27 July 2009 and 04 October 2010, respectively.

## **Review**

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

## **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by March 27, 2012. The resubmitted labeling will be used for further labeling discussions.

---

Regulatory Project Manager

Date

---

Chief, Project Management Staff

Date

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

**Sponsor has not requested a waiver for the highlights section**

- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Name of drug product is not in upper case and statement is duplicated

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and

must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) – removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

Statement is duplicated

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,”

must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Sponsor listed specific date

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**
  - A horizontal line must separate the TOC and FPI.
  - The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

Term “adverse events” is used

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Statement not included

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling.

The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA M BENJAMIN  
03/05/2012

RICHARD W ISHIHARA  
03/07/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203284 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Ravicti Established/Proper Name: glycerol phenylbutyrate (HPN-100) Dosage Form: liquid Strengths: 1:1		
Applicant: Ucylyd Pharma Inc. Agent for Applicant (if applicable): Hyperion Therapeutics		
Date of Application: 12/23/2011 Date of Receipt: 12/23/2011 Date clock started after UN:		
PDUFA Goal Date: 10/23/2012	Action Goal Date (if different):	
Filing Date: 02/21/2012	Date of Filing Meeting: 02/01/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): adjunctive therapy for chronic management of adult and children (6-17 years of age) with urea cycle disorders		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): IND 73480				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
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<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>																		

<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 3  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
If electronic submission, does it follow the eCTD guidance? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			<b>X</b>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Submission is electronic and available in the EDR.

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>			X	

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent: QT consult</i>	X			
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> 01/14/2009  <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 12/07/2010  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 6/30/2009  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 1, 2012

**BLA/NDA/Supp #:** NDA 203284

**PROPRIETARY NAME:** Ravicti

**ESTABLISHED/PROPER NAME:** glycerol phenylbutyrate

**DOSAGE FORM/STRENGTH:** liquid/ 1:1

**APPLICANT:** Ucyclid Pharma Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** adjunctive therapy for chronic management of adults (6-17 years old) with urea cycle disorders

**BACKGROUND:** Ravicti (glycerol phenylbutyrate) liquid is a new molecular entity that provides for adjunctive therapy for chronic management of adults and children (6-17 years of age) with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH deficiency). Ravicti was granted orphan designation and fast track designation on 27 July 2009 and 04 October 2010, respectively.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Richard Ishihara	N
Cross-Discipline Team Leader (CDTL)	Lynne Yao		Y
Clinical	Reviewer:	Tamara Johnson / Nancy Snow	Y
	TL:	Lynne Yao	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		

	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Insook Kim	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hamid Shafiei	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Zhong Li	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Anne Tobenkin	N
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Reema Mehta	Y
	TL:	Kendra Worthy	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Khairy Malek	N
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers Pharmacometrics	Kevin Krudy		Y
Other attendees	Donna Griebel, Andrew Mulberg, Joyce Korvick, Chantal Philips		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
Signatory Authority: Office level - TBD	
21 <sup>st</sup> Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	<ul style="list-style-type: none"> <li>notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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Regulatory Project Manager

Date

---

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

JESSICA M BENJAMIN  
03/05/2012

RICHARD W ISHIHARA  
03/07/2012

# DSI CONSULT: Request for Clinical Inspections

**Date:** February 17, 2012

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Tamara Johnson/Medical Officer, Nancy Snow/Medical Officer, and Lynne Yao/Medical Team Leader, Division of Gastroenterology and Inborn Errors Products

**From:** Jessica Benjamin, Senior Regulatory Health Project Manager/ Division of Gastroenterology and Inborn Errors Products

**Subject:** **Request for Clinical Site Inspections**

## I. General Information

Application#: NDA-203284/S-000

Applicant/ Applicant contact information (to include phone/email):

Ucyclyd Pharma (US Agent: Hyperion Therapeutics)

Drug Proprietary Name: Ravicti (glycerol phenylbutyrate; HPN-100)

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

Adjunctive therapy for chronic management of adults and pediatric patients  $\geq 6$  years of age with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (hyperornithinemia–hyperammonemia–homocitrullinuria [HHH] syndrome, also referred to as ornithine translocase deficiency).

PDUFA: **October 23, 2012**

Action Goal Date:

Inspection Summary Goal Date: **September 18, 2012 (Primary Reviews Due)**

DSI Consult  
version: 5/08/2008

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID*</b>	<b>Number of Subjects</b>	<b>Indication</b>
<b>01</b> Brendan Lee, MD, PhD Department of Molecular and Human Genetics One Baylor Plaza Room 814 Mail Code 225 Houston, TX 77030	HPN-100-006 HPN-100-005 UP 1204-003	13 0 6	Adjunctive therapy for chronic management of adults and pediatric patients ≥ 6 years of age with urea cycle disorders
<b>05</b> George A. Diaz, MD, PhD Mount Sinai School of Medicine Department of Genetics and Genomic Sciences, Box 1498 One Gustave L. Levy Place New York, NY 10029	HPN-100-006 HPN-100-005 UP 1204-003	14 2 5	Same as above
<b>03</b> William J. Rhead, MD, PhD Children’s Hospital of Wisconsin Genetics Center, MS 716 9000 West Wisconsin Avenue Milwaukee, WI 53226	HPN-100-006 9 HPN-100-005 3 UP 1204-003 4	9 3 4	Same as above

\* Total number of patients enrolled: HPN-100-006 = 46, HPN-100-005 =11, UP 1204-003 = 14

**III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

***Rationale for DSI Audits***

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See\*\*\* at end of consult template for DSI's thoughts on things to consider in your decision making process*

OSI consult for clinical site inspection is requested for three clinical sites involved in phase 2 and 3 trials in support of this NDA. The three clinical sites selected for inspection (#1, 3, and 5) enrolled 50% or more of the patient population of the above listed efficacy trial protocols. As the proposed drug indication is to treat a rare metabolic disease, all efficacy protocols were small studies enrolling less than 50 patients. Therefore, data from these three clinical sites have substantial potential to influence efficacy results for this NDA. It should be noted that there is no specific concern for scientific misconduct at any of these sites. Additionally, none of the investigators participating in any of the clinical trials had significant financial interests to disclose.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact *Jessica Benjamin RPM* at 301-796-3924, *Tamara Johnson, Medical Officer* at 301-796-1522, or *Nancy Snow, Medical Officer* at 301-796-1402.

Concurrence: (as needed)

- \_\_\_\_\_ Medical Team Leader
- \_\_\_\_\_ Medical Reviewer
- \_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for DSI Audit**

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
  - Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
  - Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity or original biological product?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA M BENJAMIN  
02/17/2012