

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203284Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Donna Griebel, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA</b>	203284
<b>Applicant Name</b>	Hyperion Therapeutics, Inc.
<b>Date of Submission</b>	December 23, 2011
<b>PDUFA Goal Date</b>	January 23, 2013 Action Date: February 1, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Ravicti/ glycerol phenylbutyrate
<b>Dosage Forms / Strength</b>	Liquid for oral administration 1.1 g of glycerol phenylbutyrate (GPB) in 1 ml of Ravicti® (equivalent to 1.02 g phenylbutyrate)
<b>Proposed Indication(s)</b>	Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders (UCD) 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.
<b>Action/Recommended Action for NME:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Nancy Snow, DO/Melanie Blank, MD
Statistical Review	Behrang Vali, MS/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/David Joseph, PhD
CMC Review	Hamid Shafiei, PhD/Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Insook Kim, PhD/Sue Chih Lee, PhD
DPDP/OPDP	Kathleen Klemm
DSI	K. Malek, MD/Susan Leibenhaut, MD/Susan Thompson, MD
CDTL Review	Melanie Blank, MD
OSE/DMEPA	Lubna Merchant, PharmD, MS/Kellie Taylor, PharmD, MPH/Carol Holquist, RPh
OSE/DRISK	Medication Guide:Latonia Ford, RN, BSN, MBA/LaShawn Griffiths, MSHS-PH, BSN, RN/ Barbar Fuller, RN, MSN, CWOCN Proposed REMS: Yasmin Choudhry, MD/Kendra

Division Director Review

	Worthy, Pharm D./Claudia Manzo, Pharm.D.
OSE/DPV	Thang La, PharmD, BCPS/Ann Mackey, RPh, MPH/Shewit Bezabeh, MD, MPH/Linda Scarazzini, MD, RPh
PMHS	Alyson Karesh, MD/Hari Cheryl Sachs, MD/ Jeanine Best/Melissa Tassinari, PhD/Lynne Yao, MD
Pediatric Ethicist/Office of Pediatric Therapeutics, OC	Michelle Roth-Cline, MD, PhD/Robert Nelson, MD, PhD
SEALD	Eric Brodsky, MD/Jeanne Delasko/Laurie Burke
Interdisciplinary Review Team for QT Studies	J. Zhang/Q. Dang/D. Marathe/N. Mehrotra/M. Fiszman/N.Stockbridge

OND=Office of New Drugs  
 OPDP=Office of Prescription Drug Promotion  
 OC= Office of the Commissioner  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DPDP=Division of Professional Drug Promotion  
 DSI=Division of Scientific Investigations  
 DRISK= Division of Risk Management  
 CDTL=Cross-Discipline Team Leader  
 PMHS=Pediatric and Maternal Health Staff

## Division Director Summary Review

### 1. Introduction

Hyperion Therapeutics, Inc. submitted the New Drug Application (NDA) for RAVICTI™ (glycerol phenylbutyrate) on December 23, 2011 pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the proposed indication:

“Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders (UCD) 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.”

Phenylbutyrate, the active pharmaceutical ingredient, is not a new molecular entity (NME). Buphenyl (sodium phenylbutyrate) was approved in 1996 and is marketed with the following very lengthy indication. I have bolded the words that most clearly reflect an actual indication:

**“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). It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.** It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. (See Nutritional Supplementation subsection of the DOSAGE AND ADMINISTRATION section.) Previously, neonatal-onset disease was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogs. However, with hemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate, and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in newborns diagnosed after birth but within the first month of life is almost 80%. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy. Patients with neonatal-onset disease have a high incidence of mental retardation. Those who had IQ tests administered had an incidence of mental retardation as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (4/7 patients tested). Retardation was severe in the majority of the retarded patients. In patients diagnosed during gestation and treated prior to any

episode of hyperammonemic encephalopathy, survival is 100%, but even in these patients, most subsequently demonstrate cognitive impairment or other neurologic deficits. In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who recover from hyperammonemic encephalopathy and are then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate is 98%. The two deaths in this group of patients occurred during episodes of hyperammonemic encephalopathy. However, compliance with the therapeutic regimen has not been adequately documented to allow evaluation of the potential for BUPHENYL and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonemic encephalopathy if carefully adhered to. The majority of these patients tested (30/46 or 65%) have IQ's in the average to low average/borderline mentally retarded range. Reversal of pre-existing neurologic impairment is not likely to occur with treatment and neurologic deterioration may continue in some patients. Even on therapy, acute hyperammonemic encephalopathy recurred in the majority of patients for whom the drug is indicated. BUPHENYL may be required life-long unless orthotopic liver transplantation is elected.”

In keeping with multiple interactions with the Division during the clinical development of Ravicti, including a SPA agreement, the safety and efficacy data submitted in support of the NDA hinge on a trial conducted to establish noninferiority of Ravicti to the approved Buphenyl (sodium phenylbutyrate) product in control of venous ammonia level, based on 24-hour AUC of ammonia ( $AUC_{NH_3}$ ). This trial (Study 006), which was conducted in adult patients with UCD, was essentially designed to demonstrate bioequivalence of the two products for the PD marker,  $AUC_{NH_3}$ , specifically focusing on the upper bound of the confidence interval, i.e., the  $AUC_{NH_3}$  ratio of the geometric means for Ravicti/Buphenyl must not exceed 1.25. Ammonia levels were considered an acceptable endpoint to establish efficacy, since high serum ammonia levels are known to cause serious morbidity and mortality in patients with urea cycle disorders (UCD). Ammonia was utilized as an endpoint to support the 2010 regular approval of Carbaglu for the UCD, N-acetylglutamate synthase (NAGS) deficiency.

Phenylbutyrate has been a key component of the armamentarium for managing UCDs for decades. Major review issues identified in this NDA for Ravicti were related to knowledge gaps also associated with sodium phenylbutyrate at the time of its approval, which are reflected in the Buphenyl label. Those issues include:

- 1) There is an absence of a clear methodology for defining a starting dose in an individual patient. Buphenyl product labeling states, “The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450 – 600 mg/kg/day in patients weighing less than 20 kg, or 9.9 – 13.0 g/m<sup>2</sup>/day in larger patients.” The key efficacy trial submitted in support of the Ravicti NDA (Study 006) evaluated patients who were not treatment naïve, and were on a stable dose of sodium phenylbutyrate. Patients enrolled in other trials submitted to this NDA were also merely converted from their stable dose of Buphenyl, with the exception of only 6 treatment naïve patients (two of whom developed neurological treatment emergent adverse events that led to dose reduction and discontinuation). The relative absence of data on how to initiate Ravicti in treatment

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