CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	203284
Applicant Name	Hyperion Therapeutics, Inc.
Date of Submission	December 23, 2011
PDUFA Goal Date	January 23, 2013 Action Date: February 1, 2013
Proprietary Name / Established (USAN) Name	Ravicti/ glycerol phenylbutyrate
Dosage Forms / Strength	Liquid for oral administration 1.1 g of glycerol phenylbutyrate (GPB) in 1 ml of Ravicti® (equivalent to 1.02 g phenylbutyrate)
Proposed Indication(s)	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.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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

	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_{NH3}). 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_{NH3}, specifically focusing on the upper bound of the confidence interval, i.e., the AUC_{NH3} 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^2/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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.