CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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Cross-Discipline Team Leader Review

Date	January 22, 2013
From	Melanie Blank, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA-203284
Applicant	Hyperion Therapeutics, Inc.
Date of Submission	December 23, 2011
PDUFA Goal Date	January 23, 2013
Proprietary Name / Established (USAN) names	Ravicti/ Glycerol Phenylbutyrate (HPN-100)
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) Usual Dose: 4.5-11.2 mL/m^2/day (5.0-12.4 g/m^2/day) by mouth divided into three equal doses with meals
Proposed Indication(s)	Ravicti is indicated as 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.
Recommended:	*Approval*

1. Introduction

Hyperion Therapeutics, Inc. submitted the New Drug Application (NDA) for RAVICTI™ (glycerol phenylbutyrate; HPN-100) on December 23, 2011 pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations. Since phenylbutyrate is the active pharmaceutical ingredient, and is an approved drug, glycerol phenylbutyrate is not a New Molecular Entity (NME).

After a thorough multidiscipline review, my recommendation, along with the review team's recommendation, is for approval of Ravicti (HPN-100, glycerol phenylbutyrate) as an adjunct to dietary management and amino acid supplementation when indicated for the chronic management of patients with urea cycle disorders (UCDs) in patients ≥ 2 years of age when dietary management alone is insufficient. Patients with N-acetylglutamate synthase deficiency

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(NAGS) were not included in the clinical trials. Carglumic acid (Carbaglu) was approved for NAGS deficiency based on the ammonia levels of patients who were treated with and without concomitant alternative pathway nitrogen binding agents including sodium phenylbutyrate which has the same active moiety as Ravicti. In the carglumic acid label it is stated in the Dosing and Administration section that, "concomitant administration of other ammonia lowering therapies is recommended." Therefore, it is prudent to be state in the label under limitations of use that, "Safety and efficacy for treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established." Another limitation of use is that RAVICTI is not indicated for treatment of acute hyperammonemia in patients with UCDs.

HPN-100 was granted orphan designation for UCDs on May 5, 2006. The review cycle was originally a standard 10 month cycle; however this was later amended to a 13 month review cycle after the submission of data from Study HPN-100-012 switch over (SO) and Study HPN-100-012 safety extension (SE) in children between 2 months and 5 years of age.

It is apparent from the review of the studies and data that were submitted as part of this NDA that there is sufficient evidence to conclude that HPN-100 is as effective as Buphenyl, the approved standard-of-care for patients with UCDs for controlling serum ammonia $AUC_{0\text{-}24}$. The efficacy of HPN-100 was demonstrated in one adequate and well-controlled, non-inferiority design study in adults with UCDs (HPN-100-006), using a surrogate endpoint (serum ammonia $AUC_{0\text{-}24}$) which was agreed upon in a special protocol assessment (SPA) for the pivotal study issued on July 6, 2009. Serum ammonia control has been the endpoint for the other ammonia lowering medications (see section titled, "CURRENT TREATMENTS FOR UCDS" starting on p. 8). Chronically and intermittently acute serum ammonia levels account for the cerebral palsy, psychiatric illness, developmental delays and neurocognitive delays and degeneration that occur in UCDs. Occasionally patients develop seizures. Morbidity and mortality in these disorders correlate with the duration and severity of hyperammonemic episodes.[1,2]

The neurotoxic effect of ammonia is well recognized; although the manner by which it exerts its effects upon the central nervous system is not very well understood. Its acute effects include increased blood–brain barrier permeability, depletion of intermediates of cell energy metabolism, and disaggregation of microtubules.[3] The effects of chronic, mildly elevated ammonia may include alterations of axonal development and alterations in brain amino acid and neurotransmitter levels.[4,5] In models of brain edema, where lethal doses of ammonia are

[1] Scaglia, F et al (2004), Clinical Consequences of Urea Cycle Enzyme Deficiencies and Potential Links to Arginine and Nitric Oxide Metabolism, Jl of Nutr, 134 (10), 27755-27825

[2] Batshaw, M. L., Roan, Y., Jung, A. L., Rosenberg, L. A. & Brusilow, S. W. (*1980*) Cerebral dysfunction in asymptomatic carriers of ornithine transcarbamylase deficiency. N. Engl. J. Med. 302*:*482-485.

[3] Butterworth, R. F. (1998) Effects of hyperammonaemia on brain function. J. Inherit. Metab. Dis. 21(Suppl. 1)*:*6-20.

[4] Bachmann, C. (2002) Mechanisms of hyperammonemia. Clin. Chem. Lab. Med. 40*:653*-662.

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administered, glial fibrillary acidic protein is reduced[6] and glutamine is increased,[7] preceded by an increase in blood flow[8]. It is not known whether nitric oxide (NO) production plays a role in such an increase. The arginine recycling enzymes are induced in astrocytes by ammonium, possibly originating NO via inducible NO synthase or neuronal NO synthesis (nNOS)[9]. The stimulated nNOS might produce O_2^-, which combines with NO to form the highly toxic peroxynitrites.[10]

For these reasons, serum ammonia control over a 24 hour period was considered to be a reasonable primary endpoint. In addition, other drugs for UCDs have been approved on the basis of ammonia control: Buphenyl (sodium phenylbutyrate) which has the same active moiety as Ravicti, and Carbaglu (carglumic acid).

There were supportive findings from other uncontrolled studies in children age 2 years to 17 years and in adults that demonstrated maintenance of ammonia control. HPN-100 was successful at preventing hyperammonemic crisis in most UCD patients, a finding that would be unexpected in the absence of effective therapy.

There are certain characteristics of HPN-100 and the development program that provide support for an approval decision based on a single trial. HPN-100 has the same active moiety as sodium phenylbutyrate (NaPBA), Buphenyl®, a drug that has been approved since 1996 and used for decades for the treatment of UCDs on the basis of its ability to activate an alternative pathway for ammonia metabolism. The pivotal study was a multicenter trial (22 centers, all in U.S. or Canada) where no one center drove the results of the trial. There was consistency of results across patients of different ages and underlying enzyme deficiencies, and while there was not a statistically persuasive finding since superiority was not achieved, the non-inferiority margin was met by a wide margin (point estimate of 1.04 with a 0.85- 1.25

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[5] Braissant, O et al, (2002) Ammonium-induced impairment of axonal growth is prevented through glial creatine. J. Neurosci. 22:9810-9820.

[6] Belanger, M et al, (2002) Loss of expression of glial fibrillary acidic protein in acute hyperammonemia. Neurochem. Int. 41:155-160.

[7] Cooper, A. J. (2001) Role of glutamine in cerebral nitrogen metabolism and ammonia neurotoxicity. Ment. Retard. Dev. Disabil. Res. Rev. 7:280-286.

[8] Larsen, et al, (2001) Cerebral hyperemia and nitric oxide synthase in rats with ammonia-induced brain edema. J. Hepatol. 34:548-554.

[9] Braissant, O., Gotoh, T., Loup, M., Mori, M. & Bachmann, C. (1999) L-arginine uptake, the citrulline-NO cycle and arginase II in the rat brain: an in situ hybridization study. Brain Res. Mol. Brain Res. 70:231-241.

[10] Demchenko, I. T., Atochin, D. N., Boso, A. E., Astern, J., Huang, P. L. & Piantadosi, C. A. (2003) Oxygen seizure latency and peroxynitrite formation in mice lacking neuronal or endothelial nitric oxide synthesis. Neurosci. Lett. 344:53-56.

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noninferiority/ bioequivalence margin). Also, there was a statistically significant correlation between urinary phenylacetylglutamine (U-PAGN)$_{24\text{-hour Excr}}$ (which is the nitrogenated active metabolite of HPN-100), and NH3$_{24\text{-hour AUC}}$ observed at steady state which was a key secondary endpoint determined through the pre-specified Hochberg's multiplicity adjustment procedure. This relationship would not be expected if HPN-100 was not the reason for ammonia control.

There was an adequate safety database: 268 subjects received at least one dose of HPN-100; The database included 112 UCD patients with deficiencies in carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (ARG) or the mitochondrial transporter ornithine translocase (HHH). 68 patients, ages 6 years to 75 years old with UCDs had completed 12 months of HPN-100 by the time of the NDA submission. The 120-day safety update included patients between 2 months to 5 years of age. The mean exposure for the < 5 year old group at the time of the 120-day safety update was 3 ½ months (maximum 7 months). There were no deaths in UCD patients, few withdrawals, few SAEs and multiple mild to moderate nonserious AEs that could partly be due to the patients' underlying diseases. Considering the persuasive findings on serum ammonia, the safety profile is acceptable.

The deficiencies of the application, enumerated below, can be handled with labeling and PMRs.

1. Lack of information regarding safety and efficacy in patients under two months of age

   Recommendation: Contraindicate Ravicti in this population with an explanation regarding the immature pancreatic exocrine function in patients less than 2 months who may or may not have other sources such as salivary lipases or lipases from breast milk that would facilitate sufficient absorption of Ravicti. The applicant has agreed to a postmarketing requirement (PMR) to study children under 2 months. These children should be studied under intensively monitored conditions.

   Hyperion-Proposed PMR Language: Hyperion commits to a study to assess safety, pharmacokinetics (b) (4) during Ravicti treatment in pediatric UCD patients less than 2 months of age (b) (4)

   Information from this study will be submitted annually (in annual reports) with a final report submission by the end of 2017. The proposed timetable for this study is as follows:

   Final Protocol Submission: April 1, 2013
   Study Completion Date: April 1, 2017
   Final Report Submission: December 1, 2017

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