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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 22, 2013
From	Melanie Blank, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA-203284
Supplement#	
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:	<i>Approval</i>

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

• Cross Discipline Team Leader Review • Melanie Blank, MD, DGIEP • NDA 203284 • Standard review for Ravicti™ (glycerol phenylbutyrate) liquid for oral administration • Class: Nitrogen Binding

(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_{0-24} . 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_{0-24}) 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.

administered, glial fibrillary acidic protein is reduced⁶ and glutamine is increased,⁷ preceded by an increase in blood flow⁸. 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 synthase (nNOS)⁹. The stimulated nNOS might produce O₂⁻, 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

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.

noninferiority/ bioequivalence margin). Also, there was a statistically significant correlation between urinary phenylacetylglutamine (U-PAGN)_{24-hour Excr} (which is the nitrogenated active metabolite of HPN-100), and NH₃_{24-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

The review team is going to request a delay for the final protocol submission as it may take longer to agree on the details of the protocol.

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

2. Very few data on patients in the age category of 2 months to 2 years were included in the NDA. The numbers of patients in this age range (4) and the timing of assessments were insufficient to conduct an adequate exploration of an effective dosing algorithm (by mg/kg vs. mg/m²) and the association between adverse events and Ravicti metabolite (in particular, PAA) levels. Two of the four patients in this age-range had PAA levels ~ 500 µg/mL when on Buphenyl or HPN-100 which may be associated with neurotoxicity.

PAA toxicity, with neurological and gastrointestinal manifestations has been demonstrated with IV administration of PAA. The symptoms at PPA levels of ~500 µg/mL were somnolence, emesis and lethargy in patients with cancer who received IV PAA. More severe toxicity (confusion and psychomotor depression) occurred in patients with mean peak PAA level of 682 µg/mL¹¹. Overdose of IV PAA in children has been reported to cause coma and death.¹² Levels of PAA in the children who had coma or died were > 1000 µg/mL.

In addition to a neurotoxicity signal, there is also an animal carcinogenicity signal (see Pharmacology-Toxicology section). For these reasons, it is important to understand the safety and efficacy of HPN-100 in this patient population.

Recommendation: The clinical pharmacology review states that it is not possible from data provided in this NDA to provide safe and effective dosing instructions for patients < 2 years of age. Therefore, it is advisable to change the indication so that Ravicti is approved for patients with UCDs ≥2 years of age. Two PMRs in children between 2 months and 2 years of age were proposed to Hyperion and accepted. Hyperion agreed to commit to this PMR as worded below.

FDA Proposed PMR Language: Study in pediatric patients aged 2 months to 2 years with Urea Cycle Disorders. Patients when they are no longer in the acute hyperammonemic phase will be started on Ravicti. Ammonia levels and phenylacetic acid (PAA) levels will be checked on a fixed schedule and at the time of adverse events.

The FDA Proposed Language for the second PMR: Conduct pharmacokinetic studies in pediatric patients from birth to less than 2 years of age with Urea Cycle Disorders. PK of glycerol phenylbutyrate and its metabolites (PBA, PAA and PAGN) must be characterized.

¹¹ Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. Cancer 1995;75:2932-8.

¹² Parphanphoj et al (2000), Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring after the treatment of acute hyperammonemia, J. Inherit. Metab. Dis 23: 129-36.

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission for both PMRs: April 1, 2013

Study Completion Date: April 1, 2016 for the overall study and April 1, 2017 for the PK study

Final Report Submission for the overall study: December 1, 2016 and December 1, 2017 for the PK study.

The review team is going to request a delay for the final protocol submissions as it may take longer to agree on the details of the protocol.

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

3. In clinical studies in support of NDA203284 most patients were on an established dose of Buphenyl (sodium phenylbutyrate) prior to enrolling in the trial. The dose of Ravicti administered to most patients was determined by a formula used to provide equal dose of phenylbutyrate (PBA) as they had been receiving from Buphenyl, sodium PBA. Therefore there is limited experience with dosing of Ravicti in treatment naïve patients. A concerning safety signal was that 2 of the 6 patients who were started on Ravicti without first attaining a stable dose of Buphenyl had neurological TEAEs that lead to dose reduction and discontinuation. Ravicti has the same active moiety as Buphenyl. Therefore, it is considered safe for the purpose of approval to initiate dosing with Ravicti. However, the signal of neurotoxicity that was seen in the 2 patients who were not already stabilized on Buphenyl raises the concern that treatment naïve patients may not tolerate de novo dosing with this product as well as they do with Buphenyl.

Recommendation: The review team has agreed that dosing instructions in the label will have to be divided into several sections as follows:

2.1 Important Instructions

RAVICTI should be prescribed by a physician experienced in the management of UCDs. Instruct patients to take RAVICTI with food and to administer directly into the mouth via oral syringe or dosing cup. See the instructions on the use of RAVICTI by nasogastric tube or g-tube [see *Dosage and Administration* (2.6)].

The recommended dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to phenylbutyric acid are different [see *Dosage and Administration* (2.2, 2.3)]. For both subpopulations:

- Give RAVICTI in three equally divided dosages, each rounded up to the nearest 0.5 mL
- The maximum total daily dosage is 17.5 mL (19 g)
- 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).

2.2 Switching from Sodium Phenylbutyrate to RAVICTI

Patients switching from sodium phenylbutyrate to RAVICTI should receive the dosage of RAVICTI that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of RAVICTI (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8

2.3 Initial Dosage in Phenylbutyrate Naïve Patients

The recommended dosage range, based upon body surface area, in patients naïve to phenylbutyrate (PBA) is 4.5 to 11.2 mL/m²/day (5 to 12.4 g/m²/day). For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m²/day.

In determining the starting dosage of RAVICTI in treatment naïve patients, consider the patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. Given that approximately 47% of dietary nitrogen is excreted as waste and 70% of an administered PBA dose will be converted to urinary phenylacetylglutamine (U-PAGN), an initial estimated RAVICTI dose for a 24 hour period is 0.6 mL RAVICTI per gram of dietary protein in 24 hours.

2.4 Dosage Adjustment and Monitoring

Adjustment based on Plasma Ammonia: Adjust the RAVICTI dosage to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) (according to age).

Adjustment based on Urinary Phenylacetylglutamine: If available, U-PAGN measurements may be used to help guide RAVICTI dose adjustment. Each gram of U-PAGN excreted over 24 hours covers waste nitrogen generated from 1.4 gram of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dose should be adjusted upward. Consider a patient's use of concomitant medications, such as probenecid, when making dosage adjustment decisions based on U-PAGN. Probenecid may result in a decrease of the urinary excretion of PAGN [see *Drug Interactions (7.2)*].

Adjustment based on Plasma Phenylacetate: If available, measurements of the plasma PAA levels may be useful to guide dosing if symptoms of vomiting, nausea, headache, somnolence, confusion or sleepiness are present in the absence of high ammonia or intercurrent illness. Ammonia levels must be monitored closely when changing the dose of RAVICTI [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

2.5 Dosage Modifications in Patients with Hepatic Impairment

For patients with moderate to severe hepatic impairment the recommended starting dosage is at the lower end of the range [see *Warnings and Precautions (5.1, 5.4)* and *Clinical Pharmacology (12.3)*].

2.6 Preparation for Nasogastric Tube or Gastrostomy tube Administration

For patients who have a nasogastric tube or gastrostomy tube in place, administer RAVICTI as follows:

- Utilize an oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into to the tip of the g-tube/nasogastric tube
- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Flush once with 30 mL of water and allow the flush to drain.
- Flush a second time with an additional 30 mL of water to clear the tube.

To address the concerns that initial dosing and titration based on the instructions from the label may not be safe and effective, a PMR has been stipulated and Hyperion has agreed to fulfill it.

The FDA proposed language for the PMR was as follows: Randomized controlled clinical trial to assess the safety and efficacy of initiating and titrating Ravicti in treatment naïve patients with UCDS

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission: December 1, 2013

Study Completion Date: June 1, 2016

Final Report Submission: March 30, 2017

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

4. Inconclusive Thorough QT (TQT) study

Recommendation: The IRT-QT recommended that a repeat study should be performed because of lack of assay sensitivity in the original study or there should be language in the label to explain the lack of assay sensitivity. For there to be assay sensitivity, the moxifloxacin effect on QT interval must show an upslope from normal to elevated. This upslope was not demonstrated. The QT interval was high from the first ½ hour which was the first data point captured in the report. Furthermore, the moxifloxacin effect on QT came down from 10 ms to 5 ms very rapidly and stayed there for most of the 24 hour test period. This is unusual. The review team agreed with the IRT-QT's recommendation and proposed language to the applicant for use in the QT section of the label:

The effect of multiple doses of Ravicti 13.2 g/day and 19.8 g/day (approximately 69% and 104% of the maximum recommended daily dosage) 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. However, assay sensitivity was not established in this study. Therefore, an increase in mean QTc interval of 10 ms cannot be ruled out.

The applicant was informed that they will need to repeat a thorough QT study with assay sensitivity or they will need to demonstrate that there was an upslope in the moxifloxacin arm from a normal length to a prolonged length to have this language removed from the label.

5. The risks of treating breast-feeding patients are not known. There is a concern of effects on unborn fetuses and neonates because of neurotoxicity findings seen with Buphenyl in rat pups given HPN-100 in their food, and carcinogenicity findings in a 2-year rat carcinogenicity study which the Cancer Assessment Committee deemed as being drug-related. It is unknown if PBA, PAA, or PAGN pass into the breast milk. Ravicti is expected to be used by women of reproductive age and data on exposure of the drug via breast milk is needed.

Recommendation: Appropriate language will be placed in the label for pregnant and breast-feeding patients and encouragement to participate in the Ravicti Urea Cycle Disorders registry. We are in the process of having the PMHS team consult to help provide the appropriate language in the label. PMHS is also being asked to advise the applicant about conducting an appropriately designed post-marketing study to assess the quantity of PBA, PAA, or PAGN that passes into breast milk.

6. CYP enzyme interactions. 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.

Recommendation: Since chronic administration of Ravicti is expected for UCD patients, the evaluation of the potential in vivo drug interaction with concomitant medications that may compete for CYP enzymes is warranted.

The FDA proposed language for the PMR: In vivo drug interaction study to evaluate the effect of Ravicti on the pharmacokinetics of a drug that is a sensitive substrate of CYP3A4/5 (e.g., midazolam).

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission: September 30, 2013

Study Completion Date: March 31, 2014

Final Report Submission: July 1, 2014

7. Patients with advanced hepatic disease had elevated phenylacetate (PAA)/Phenylacetylglutamine (PAGN) ratios because they do not convert PAA to PAGN as quickly as a person without advanced hepatic disease. Patients with advanced hepatic impairment are therefore at risk of developing PAA toxicity. There were 5 patients in

the hepatic impairment studies who died. Their deaths may have been related to their underlying disease. PAA toxicity was not evaluated in these patients. 2 were known to be on HPN-100, the 3 others were in an ongoing study (HPN-100-008 Part B) that is still blinded.

Recommendation: Labeling in the Dosage and Administration Section (2.4) and in the Special Populations Section 8.6 will be placed to advise practitioners to start patients with hepatic disease at the lower end of the dosing range (4.5 mL/m²/day). There will also be a warning in the Warnings and Precautions in Section 5.5 for patients with advanced hepatic disease explaining that they are at increased risk for PAA toxicity.

8. There are unknown benefits and risk of treating patients with renal disease.

Recommendation: In section 12.3 Pharmacokinetics the following language has been proposed to Hyperion:

Renal Impairment

The pharmacokinetics of Ravicti in patients with impaired renal function including end-stage renal disease (ESRD) or on hemodialysis have not been studied.

2. Background

Urea Cycle Disorders

The urea cycle produces arginine by *de novo* synthesis while also producing urea. Six enzymatic reactions comprise the cycle, which occurs in the liver. The first three reactions are located intramitochondrially [N-acetylglutamate synthase (NAGS), carbamylphosphate synthetase (CPS) and ornithine transcarbamylase (OTC)], and the rest are cytosolic [arginosuccinate synthetase (AS), arginosuccinate lyase (AL), and arginase (ARS)]. There is also a mitochondrial membrane transporter that can be deficient, ornithine translocase (HHH). The enzymatic substrates are ammonia, bicarbonate, and aspartate. There are also cofactors necessary for optimal enzyme activity, the most clinically important of which is N-acetyl glutamate (NAG). After each turn of the cycle, urea is formed from two atoms of nitrogen (see Fig. 1).

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Phenylacetate then combines with glutamine and is then excreted into the urine as phenylacetylglutamine. Figure from a publication by Walters and Brophy¹³

The prevalence of UCDs is estimated at 1:8,200 in the USA. The overall incidence of defects presenting clinically is estimated at approximately 1 in 45,000 live births. Using the US birth rate in 2000 of 4.06 million births¹⁴ and the incidence rate of 1:8200, it is estimated that approximately 495 patients with UCDs are born each year in the US. The prevalence of these disorders may exceed the current estimates,¹⁵ for all UCDs jointly because of unreliable newborn screening and underdiagnosis of fatal cases. From epidemiological studies,^{16,17} 50%

¹³ Walters S, Brophy PD (2009) Inborn errors of metabolism and continuous renal replacement therapy. In: Ronco C, Bellomo R, Kellum J (eds) Critical care nephrology, 2nd edn. Elsevier, Oxford, pp 1630–1633

¹⁴ Ventura SJ et al, (2004); Estimated Pregnancy Rates of the United States, 1990-2000: an update, National vital Statistics reports, 52, 23, p. 1-12

¹⁵ Brusilow SW et al, (1996), Adv Pediatr. 1996;43:127–170.

¹⁶ Bachman C, (2003), Outcome and survival of 88 patients with urea cycle disorders: a retrospective evaluation. Eur J Pediatr; 162(6):410-6.

of neonatal onset patients die in the neonatal period despite therapy. The National Institute of Health- (NIH) funded Urea Cycle Disorders Consortium (UCDC) Longitudinal Study now includes 12 major centers in the US as well as sites in Toronto and Zurich, and has enrolled only 495 patients over the first 5 years. Of these patients, 400 are prescribed NaPBA. By birth incidence, if patients lived a full life span there would be approximately 35,000 patients in the U.S. Since many UCD patients die young, and/or have liver transplant, it is not possible to estimate the numbers of patients who currently have the disorder in the U.S. A thorough literature search did not reveal any reliable prevalence statistics. Clearly, there is a need for better natural history studies.

The first report resulting from the Longitudinal Study¹⁸ describes the patient population. One hundred eighty three participants were enrolled into the study at the time this report was written. OTC deficiency was the most frequent disorder (55% of total enrolled), followed by AL deficiency (16%) and AS deficiency (14%). Intellectual and developmental disabilities were reported by 39% of participants, learning disabilities were reported by 35%, and half had abnormal neurological examinations (including findings like tone changes, reflex abnormalities, and abnormal movements). Sixty-three percent were on a protein restricted diet, 37% were on sodium phenylbutyrate (Buphenyl) and 5% were on oral sodium benzoate. Forty-five percent of OTC deficiency participants were on L-citrulline. Most participants with AS deficiency (58%) and AL deficiency (79%) were on L-arginine. Plasma levels of branched-chain amino acids (valine, leucine and isoleucine) were reduced in patients treated with ammonia scavenger drugs (sodium phenylbutyrate and sodium benzoate). Plasma glutamine levels were higher in proximal UCD (OTC Deficiency and CPS deficiency) and in neonatal type disease.

In UCDs, there is an increase in glutamine, which transports nitrogen groups to the liver for ammonia formation within hepatic mitochondria. The presence of an enzymatic defect in the urea cycle results in the accumulation of waste nitrogen mainly as ammonia (hyperammonemia) and glutamine. When ammonia accumulates in the brain, it is highly toxic and depending on the level, may cause life-threatening encephalopathy.

Inborn errors of urea synthesis lead to an accumulation of ammonia in blood and brain and present clinically as recurrent episodes of hyperammonemic crisis manifested by vomiting, lethargy, and coma. Infants with complete enzyme deficiencies commonly present in the newborn period with hyperammonemic coma. Despite aggressive treatment with hemodialysis, the mortality in the newborn period for proximal urea cycle defects (OTC deficiency and CPS deficiency) has been reported to approach 50%.¹⁹ Survivors have developmental disabilities

Eur J Pediatr. 2003 Jun; 162(6):410-6.

¹⁷ Maestri NE et al, (1999) Neonatal onset ornithine transcarbamylase deficiency: A retrospective analysis; 134(3):268-72.

¹⁸ Tuchman M, et al, (2008) Cross-Sectional Multi-center Study of Patients with Urea Cycle Disorders in the United States Mol Genet Metab 2008 94:397-402

¹⁹ Maestri NE, Clissold D, Brusilow SW 1999 Neonatal onset ornithine transcarbamylase deficiency: a retrospective analysis. J Pediatr 134:268-272

that correlate with the number, severity, and duration of hyperammonemic crisis episodes.²⁰ Studies of children with neonatal UCDs have shown variable intellectual outcomes, based broadly on developmental quotients (DQs) or on traditional intelligence quotient (IQ) scores. A high percentage of patients with UCDs (60–80%) develop mental retardation.²¹ They also have a high incidence of ADHD (~17%), communication disorders (~13%), cerebral palsy (~3%), intellectual developmental disabilities (~39%), learning disabilities (~35%), mood disorders (~7%), other psychiatric disorders (~8%), seizure disorders (~15%), visual or hearing impairment (~13%), cerebellar findings (~10%), movement disorders (~13%), and changes in muscular tone (~25%). Neonatal onset of UCDs is associated with higher incidence of most of these disorders compared to later onset.

Partial enzyme deficiencies may present later in life, even in adulthood. Regardless of the timing of presentation, urea cycle disorders can be life-threatening. Brain edema is a common feature of ammonia toxicity. Once the fontanelles close (during the first few months of life) there is an increased risk of herniation. OTC is the most common urea cycle enzyme defect, with an incidence of 1 in 14,000, and is the only one inherited as a sex-linked trait. In heterozygous females with OTC deficiency, there may be milder symptoms. This is thought to be a consequence of the Lyon hypothesis whereby the normal gene is expressed in some of the hepatocytes and the abnormal gene is expressed in others. In fact, only 15% of heterozygous OTC deficient females are symptomatic, and most asymptomatic carriers have a normal IQ score.²² These patients may also develop hyperammonemic crises if under extreme metabolic stress.

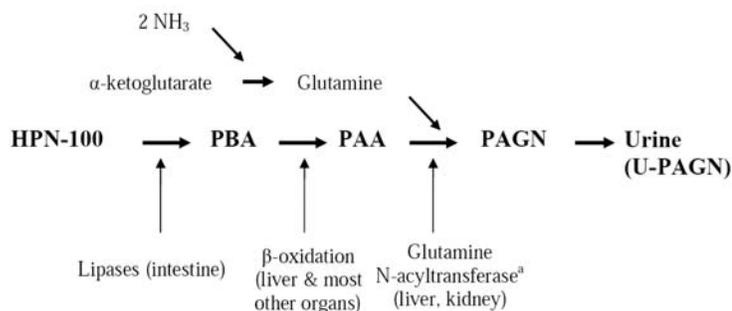
When there is a defect in the urea cycle, there are two alternative intracellular pathways by which nitrogen can be conjugated into an excretable form if provided the proper substrates (exogenously); PBA, PAA or benzoate. PBA is converted by β -oxidation to PAA which conjugates with glutamine in the liver and kidneys to form phenylacetylglutamine, via acetylation. Phenylacetylglutamine (PAGN) is excreted by the kidneys via glomerular filtration and tubular secretion. The nitrogen content of PAGN per mole is identical to that of urea (both contain two moles of nitrogen). Two moles of nitrogen are removed per mole of PAA when it is conjugated with glutamine. Similarly, preceded by acylation, benzoate conjugates with glycine to form hippuric acid, which is rapidly excreted by the kidneys by glomerular filtration and tubular secretion. One mole of hippuric acid contains one mole of waste nitrogen. Thus, one mole of nitrogen is removed per mole of benzoate when it is conjugated with glycine.

²⁰ Msall M, Monahan PS, Chapanis N, Batshaw ML 1988 Cognitive development in children with inborn errors of urea synthesis. *Acta Paediatr Jpn* 30:435–441

²¹ Msall M, Monahan PS, Chapanis N, Batshaw ML 1988 Cognitive development in children with inborn errors of urea synthesis. *Acta Paediatr Jpn* 30:435–441

²² Auron et al, Hyperammonemia in review: pathophysiology, diagnosis, and treatment, *Pediatr Nephrol* (2012) 27: 207-222.

Figure 2.5-1: Biotransformation of HPN-100 (glycerol phenylbutyrate)



NH₃ = ammonia; PAA = phenylacetic acid; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; U-PAGN = urinary phenylacetylglutamine.

^aThis conversion likely involves more than one enzyme present in liver and kidney (Moldave 1957)

Source: applicant

CURRENT TREATMENTS FOR UCDS

APPROVED DRUGS

Sodium Phenylbutyrate (NaPBA) (Buphenyl) has the same active moiety as HPN-100 (PBA) and is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of CPS, OTC, or AS. It is the only drug with marketing approval for chronic therapy of patients with UCDS aside from Carbaglu which is indicated for NAGS deficiency only. Buphenyl 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. NaPBA is a pro-drug and is rapidly metabolized to PAA. PAA is a metabolically-active compound that conjugates with glutamine via acetylation to form PAGN. PAGN then is excreted by the kidneys. Although NaPBA is widely used in patients with urea cycle disorders, its disadvantages when compared to HPN-100 are that it brings with it a high salt load (up to 2400 mg/day, high pill burden (up to 40/ day) and is unpalatable. Approval was based on the results of two pharmacodynamic endpoints: decreased plasma ammonia and glutamine levels and increased waste nitrogen excretion in the form of PAGN (1996).

Sodium Phenylacetate and Sodium Benzoate Injection (Ammonul) for management of acute episodes of hyperammonemic crisis. It is not used in the chronic management of patients with UCDS. Sodium PAA is conjugated with glutamine to form PAGN, which is excreted by the kidney. Sodium benzoate, by its acylation of glycine to hippurate and its rapid renal clearance, can remove 1 mole of waste nitrogen for each mole of benzoate administered. Approval in 2005 was based on the demonstration of improved survival in a retrospective analysis of 316 patients (1045 episodes of hospitalization). Although there have been no controlled studies, introduction of alternative pathway therapy appears to have improved both biochemical control and neurologic outcome in patients with early presentation of urea cycle disorders. Between 1972 and 2000, 217 patients were diagnosed with a UCD; 121 had neonatal onset disease and 96 had late-onset disease. Overall, outcome was poor with mortality reaching 84% (60% if males with OTC deficiency are excluded) in neonatal-onset cases and 28% in those who had late-onset forms of disease. There was a high risk of neurological

impairment in survivors.²³ In contrast, an open-label, uncontrolled, non-randomized clinical trial of Ammonul and arginine hydrochloride therapy was performed in 118 hospitals in the United States and Canada from August, 1980 to March, 2005. Overall patient survival was 84% (250 of 299 patients), while hyperammonemic episode survival was 96% (1132 of 1181 episodes). The episode survival rate was lowest (91%) for males with OTC deficiency.²⁴ Furthermore, the duration and severity of hyperammonemia strongly correlates with brain damage. This suggests that all treatments for hyperammonemia may have an impact on neurocognitive functioning.²⁵

Ammonul is used on most patients at presentation because most patients present in hyperammonemic crisis (over 100 µmol/L) as well as at times when there are exacerbations due to noncompliance with oral medications, diet or catabolic state induced by infection or another stress. There is an advantage to this treatment over others for emergency treatment in that it is IV and begins to work immediately to reduce ammonia load. It also activates both alternative pathways concurrently.

Sodium Phenylacetate and Sodium Benzoate for oral use can be obtained from compounding pharmacies. See description above for Ammonul. This product has the same ingredients as Ammonul but is compounded for chronic oral use. It is for patients who do not respond to or are intolerant of sodium phenylbutyrate. It carries a high sodium load and is even more unpalatable than sodium phenylbutyrate.²⁶

Carglumic Acid (Carbaglu), for chronic oral administration is indicated as adjunctive therapy for the treatment of acute and chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS. Carglumic acid is a synthetic structural analogue of NAG, which is an essential allosteric activator of CPS. Approval was based on a retrospective analysis of mean ammonia levels in 23 NAGS deficiency patients who received Carbaglu treatment for a median of 7.9 years. (2010). Clinical observations in the 23 patient case series were retrospective, unblinded and uncontrolled and precluded any meaningful formal statistical analyses of the data. The overall mean baseline plasma ammonia level was 271 µmol/L in a subset of 13 patients who had both well documented plasma ammonia levels prior to and after Carbaglu treatment. By day 3, normal plasma ammonia levels were attained in these 13 patients. Long-term efficacy was measured using the last reported plasma ammonia level for each of the 13 patients analyzed (median length of treatment was 6 years; range 1 to 16 years). The mean and median ammonia levels were 23 µmol/L and 24 µmol/L, respectively, after mean treatment duration of 8 years.

OTHER THERAPIES

²³ M.C. Nassogne et al, (2005), Urea cycle defects: management and outcome, J. Inherit. Metab. Dis. 28 (3) 407–414.

²⁴ G.M. Enns et al, (2007), Survival after treatment with phenylacetate and benzoate for urea-cycle disorders, N. Engl. J. Med. 356 (22) 2282–2292.

²⁵ Msall M et al, (1984), Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. N Engl Med. 310(23):1500-5.

²⁶ Batshaw, M, MacArthur R, Tuchman M, Alternative pathway therapy for urea cycle disorders: Twenty years later, JI Ped, 2001:138,1:S47-S55.

Hemodialysis is recommended when brain damage or death is imminent and for those patients whose plasma ammonia levels fail to fall below 150 $\mu\text{mol/L}$ or by more than 40% within 4 to 8 hours after receiving Ammonul IV.

Protein Restriction: Infants with neonatal-onset CPS and OTC deficiencies initially receive a daily dietary protein intake limited to approximately 1.6 g/kg/day for the first 4 months of life. If tolerated, the daily protein intake may be increased to 1.9 g/kg/day during this period. Protein tolerance will decrease as the growth rate decreases, requiring a reduction in dietary nitrogen intake.

Intravenous Glucose and Insulin: Required to help patient return to an anabolic state.

L-Citrulline oral supplementation is recommended for patients diagnosed with neonatal-onset deficiency of carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily intake is recommended at 0.17 g/kg/day or 3.8 g/m²/day. It has the advantage of removing one nitrogen atom while being converted to arginine.²⁷

Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 0.4 – 0.7 g/kg/day or 8.8 – 15.4 g/m²/day. It is recommended to be given by central line because it may cause tissue necrosis when there is extravasation. High-dose arginine-HCL may cause metabolic acidosis. Arginine is also useful for AS and AL enzyme deficiencies because it is converted into argininosuccinate and/or citrulline, providing an alternative pathway for waste nitrogen handling.

IV Sodium bicarbonate: To neutralize the acidifying effects of arginine hydrochloride.

Liver Transplant: The definitive treatment and recommended for most patients who have neonatal onset but not with severe neurological damage at the time of diagnosis. Liver transplantation allows the UCD patient to return to a normal diet and obviates the need for nitrogen binding therapy.

Liver transplantation should be deferred, if possible, until 3 months of age and/or 5 kg body weight to avoid the increased complications and lower survival rates observed when performed before attaining this age and weight. Ideally, it should be done before 1 year of age for best neurological outcome, especially in CPS deficiency, in OTC deficiency males, in patients with recurrent metabolic decompensations despite treatment or when treatment compliance is poor. In selected cases presenting with poor treatment compliance, diet-induced growth retardation, poor school attendance, altered psychological status or problems with familial and social integration, transplantation may be considered later, sometimes even during adolescence. OTC

²⁷ The Urea Cycle Disorders Conference Group (2001), Consensus statement from a Conference for the Management of Patients with Urea Cycle Disorders, *Jl Ped*, 138, No. 1: S1-S5.

deficiency females presenting symptoms in the first 2 years of life have a second lethality peak at 12–15 years of age and thus they should also be considered for liver transplantation.²⁸

NOVEL PROPOSED TREATMENT FOR UCDs IN THIS NDA

Glycerol PBA (**Ravicti**) is the subject of this review and is referred to throughout the review of this application as either Ravicti or HPN-100. It is a precursor of PBA, and thus a pre-prodrug. Ravicti differs from NaPBA in that it does not carry a high sodium load (sodium phenylbutyrate will deliver up to 2400 mg sodium per day), can be delivered in approximately half the volume as NaPBA, and is more palatable. The active moiety is the same for both drugs. Ravicti is distinguished from Buphenyl because there are three PBA molecules attached to a glycerol back-bone, and no sodium. For the PBA to be absorbed into the intestinal cells, the glycerol backbone has to be hydrolyzed in the small intestine by pancreatic enzymes and potentially other lipases, typically not present in neonates until about age 2 months. It is possible that salivary lipases are sufficient for the breakdown of HPN-100 in the mouths and intestines of neonates, but this has not been established. PBA is taken up by the liver cells where it breaks down to PAA which binds to the ammonia vehicle (glutamine) to form PAGN which is then excreted by the kidney.

3. CMC/Device

Each mL of liquid contains 1.1 grams of glycerol phenylbutyrate and delivers 1.02 grams of phenylbutyrate (PBA).

GPB is a colorless to pale yellow liquid. It is manufactured and supplied by two different manufacturers. The drug product is (b) (4)

. There are (b) (4)

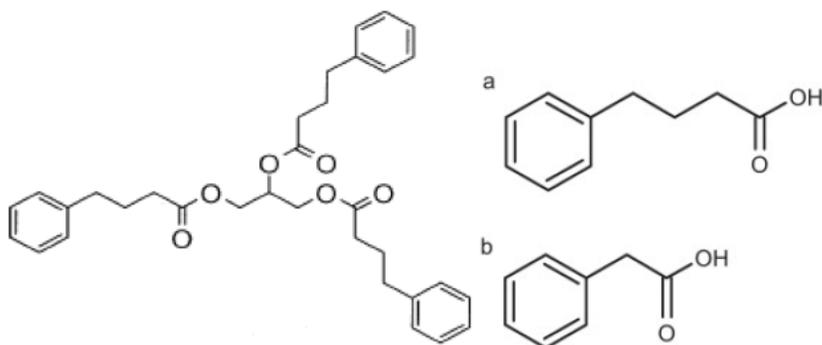


Figure 2: Structure of glycerol phenylbutyrate (HPN-100) and its metabolites (a) PBA and (b) PAA

²⁸ Johannes Häberle, (2012), *Orphanet J Rare Dis.*; 7: 32. Published online 2012 May 29.

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In the clinical trials included in this NDA, the dose of Ravicti was determined based on the molar content of PBA equivalent to Buphenyl by the following equation:

$$\text{Total daily dosage of RAVICTI (mL)} = \text{total daily dosage of sodium phenylbutyrate (g)} \times 0.86$$

The derivation of the above equation is:

1.0 grams of HPN 100 delivers 0.93 g of phenylbutyrate
1.0 gram of sodium phenylbutyrate delivers 0.88g of phenylbutyrate
 $0.88/0.93 \text{ NaPBA g} = \text{HPN-100 g}$
 $0.95\text{g NaPBA g} = 1 \text{ g HPN-100/ } 1.1 \text{ g/mL}$
 $0.95/ 1.1 \text{ NaPBA g} = \text{HPN-100 mL}$
 $0.86 \times \text{NaPBA g} = \text{HPN-100 mL}$

Each HPN-100 dose was allowed to be rounded up to the nearest 0.2 mL and administered by either disposable syringes or medication cups.

According to the Chemistry reviewer, Dr. Shafiei, “the applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, Ravicti liquid for oral administration.”

Dr. Shafiei recommended that the “1.1 g/mL glycerol phenylbutyrate “concentration be added to the label in “highlights” and the “How Supplied/Storage and Handling” Section as well as to the immediate container label and to the carton label. He also recommended that the pharmacological/ therapeutic class “Nitrogen Binder” be added to the Description section of the label. Additionally, storage conditions instructions were felt to be unsatisfactory and the following language is recommended, “Store at 20 – 25°C with excursion permitted to 15 – 30°C” and should be included in Section 16.2, Storage, the immediate container label and the carton label. The review team agreed with these recommendations which were communicated to and accepted by Hyperion.

There are no outstanding chemistry-related issues.

4. Nonclinical Pharmacology/Toxicology

Neoplastic signal in rats

In the 2-year rat carcinogenicity study, glycerol phenylbutyrate produced an increased incidence of pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma, and Zymbal’s gland carcinoma in both male and female rats, and thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp and combined polyp or sarcoma in female rats. The male rats were exposed to 650 mg/kg/day in males (4.7 times the dose of 6.87 ml/m²/day in adult male patients) and the females rats were exposed to 900 mg/kg/day (8.4

times the dose of 6.87 ml/m²/day in adult female patients). The multiples are lower for pediatric patients because the exposure is higher (3 times the dose for male pediatric patients and 5.5 times the dose of female pediatric patients). Sodium phenylbutyrate or Ammonul had no long term carcinogenicity studies done according to their labels.

The nonclinical pharmacology/ toxicology review by Dr. Ke Zhang explained that glycerol phenylbutyrate and its major metabolites are not genotoxic and that a common and likely mechanism for induction of thyroid follicular cell tumors in rodents is through hepatic microsomal enzyme induction²⁹. In support of this theory, PBA, PAA and PAGN were found to induce P450 in cultured human hepatocytes. In addition, hepatocellular hypertrophy (indicative of enzyme induction) was observed in mice and monkeys in repeat-dose toxicity studies with glycerol phenylbutyrate. Unfortunately, Hyperion did not address the question of whether glycerol phenylbutyrate or its metabolites produces enzyme induction in rats. Hyperion submitted a study that demonstrated a dose-dependent increase in liver weight (a sign of enzyme induction) in the 3-month oral toxicity study in rats, but this effect was not associated with histological findings such as hepatocellular hypertrophy that would have provided more compelling evidence of enzyme induction. While not as complete as one would like, the evidence supports the hypothesis that the rat thyroid tumors were caused by hepatic enzyme induction, a mechanism that does not appear to be relevant to the risk of thyroid tumor development in humans.³⁰

The Cancer Assessment Committee on July 17, 2012 held a meeting and concluded that the tumors seen in rats including the thyroid tumors in female rats were drug related. Dr. Zhang thought that while there may be a signal of tumorigenicity, the benefit of glycerol phenylbutyrate outweighs this risk.

Dr. Thang La from the Division of Pharmacovigilance was consulted to investigate if there were any spontaneous reports and literature for human cases of malignancy reported as a complication of NaPBA use. The AERS database and NIH PubMed did not identify any reports of malignancy as a possible adverse event.

PBA and PAA have also been found to be potent cellular differentiating and cytostatic agents in cell culture systems at plasma level concentrations similar to those utilized during the treatment of urea cycle defects.³¹ The exact anti-cancer mechanism of aromatic fatty acids is still not known. However, PBA and PAA inhibit nuclear histone deacetylation with subsequent activation of genetic transcription which is considered a major mediator in tumor growth arrest and cellular differentiation. Moreover, systemic glutamine depletion has also been reported in association to their anti-tumor effects.³²

Significant in vitro antitumor activity has been reported in prostate carcinoma, breast cancer, myeloid leukemia, Burkitt's lymphoma, and other cell lines. PAA and PBA can induce cellular

²⁹ Capen, Toxicologic Pathology, 25(1), pg. 39-48, 1997

³⁰ Capen, Toxicologic Pathology, 25(1), pg. 39-48, 1997

³¹ Samid D, Shack S, Sherman LT (1992) Phenylacetate: a novel nontoxic inducer of tumor cell differentiation. Cancer Res 52(7):1988-1992

³² Camacho L, et al, (2007) Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumors, Invest New Drugs 25:131-8.

differentiation of multi-drug-resistant breast, ovarian, and colon carcinoma cell lines. Besides their antitumor properties, PAA and PBA can also induce time and dose dependent erythroid differentiation and enhance hemoglobin *F* production.³³ PBA was found to have dose-dependent inhibitory effects on glioma cell proliferation, morphology, migration, invasiveness and *c-myc* and urokinase expression.³⁴

While the rat carcinogenicity findings (increased pancreatic, thyroid, Zymbal's glands, adrenal cortex, uterine) should be in the label, there are other data that suggest that in certain cancers (prostate, breast cancer, myeloid leukemia, and Burkitt's lymphoma, breast, ovarian and colon), PBA may be protective.

Neurotoxicity findings in animals:

The results of the repeated-dose oral toxicity studies revealed that the central nervous system was the target organ of toxicity based on clinical signs including hypoactivity, impaired equilibrium, ptosis, and shallow or labored respiration in mice, hypoactivity, impaired equilibrium, and rigid muscle tone in rats, and hypoactivity, impaired equilibrium, hunched posture, recumbency, labored respiration, and tremor in monkeys.

It should be noted that there is language in the Buphenyl label that describes rat neurotoxicity findings, "When given subcutaneously to rat pups (*after birth*), 190–474 mg/kg phenylacetate caused decreased proliferation and increased loss of neurons, and it reduced CNS myelin. Cerebral synapse maturation was retarded, and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 of the cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number."

Dr. Zhang opined in his review that the same wording regarding the neurotoxicity findings in the rat pups with NaPBA should be included in the Ravicti label because of the common biochemical pathway and metabolites of the two drugs, particularly in light of the neurotoxic findings in the repeated-dose oral toxicity studies in rats and monkeys when given high doses of HPN-100 and the neurotoxicity in rat pups exposed to PAA in the prenatal period.

Upon further discussion, it was decided that there were sufficient neurotoxicity findings from the nonclinical research done for this NDA to exclude the neurotoxicity labeling that was in the Buphenyl labeling.

Embryonic Fetal Development

A reproductive study was done in rats. The major finding was a small but statistically significant increase in embryo-lethality in the high-dose group (1.2 g/kg/day). There were

³³ Camacho L, et al, (2007) Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumors, *Invest New Drugs* 25:131-8.

³⁴ Engelhard H et al, (1998), Inhibitory effects of phenylbutyrate on the proliferation, morphology, migration and invasiveness of malignant glioma cells, *Jl of Neuro-Onc* 37: 97-108.

some fetal abnormalities, mostly due to higher incidence of tail anomalies (short, threadlike) in the high dose group. Some had skeletal abnormalities; the most common was the presence of a dose-dependent increase in incidence of a 7th cervical rib. The rabbit embryonic studies showed no treatment-related effects. Reduced motor activity and splayed limbs were also noted in the high dose group.

The fetal findings did not appear to alter Dr. Zhang's opinion of the favorable benefit/ risk profile for glycerol phenylbutyrate.

There are no unresolved pharmacology/toxicology issues.

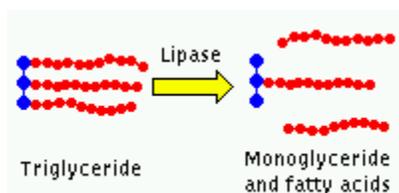
5. Clinical Pharmacology/Biopharmaceutics

PHARMACOKINETICS

Absorption

After 7 day treatment of HPN-100 in Study HPN-100-005, in UCD patients aged 6-17 years, the plasma concentrations of HPN-100 were below detection limit at all sampling time points. The same was true in adult Study UP 1204-003, but the assay method in this study may not have been valid because there was no mention of adding a stabilizer, acetonitrile, to the specimens. Acetonitrile was added to specimens when the assay was originally validated.

Interestingly, HPN-100 was recovered from serum specimens of healthy volunteers. Hyperion wasn't expecting this because HPN-100 should not be absorbed without being hydrolyzed. The applicant speculated that the specimens were contaminated with HPN-100 (which may have gotten into the acetonitrile that was used to stabilize the specimens). The median T_{max} was 5 hours which ranged from 0.5 to 48 h while median C_{max} was 72 ng/ml and ranged from 12 to 2222 ng/ml. The variability in these results supports the applicant's theory. Theoretically, the glycerol product should not be absorbed as a whole molecule. It is widely accepted that triglyceride molecules must be enzymatically digested to yield monoglyceride and fatty acids, both of which can efficiently diffuse or be transported into the enterocyte.³⁵ Hydrolysis of triglyceride into monoglyceride and free fatty acids is accomplished predominantly by pancreatic lipase. The activity of this enzyme is to clip the fatty acids at positions 1 and 3 of the triglyceride, leaving two free fatty acids and a 2-monoglyceride.



³⁵ http://www.vivo.colostate.edu/hbooks/pathphys/digestion/smallgut/absorb_lipids.html

Following the oral administration of single doses of HPN-100 to healthy participants, plasma concentrations of PBA were quantifiable in 15 out of 22 participants at the first sample time post-dose (0.25 h), indicating rapid absorption of PBA. Mean maximum plasma concentrations of PBA were attained at 2 h post-dose, followed by a rapid decline, and were below the level of quantification beyond 8 h post-dose. PAA levels were quantifiable at 1 h post-dose, reached the mean maximum at 4 h, and decreased below the limit of quantification beyond 8 h post-dose. Mean concentrations of PAGN were quantifiable at 0.5 h post-dose, and reached a maximum at 4 h. The mean terminal half-lives for PBA, PAA and PAGN were 1.9, 1.4 and 5.9 hours, respectively.

In healthy adults, the AUCs for PBA and PAA were both ~75% lower after HPN-100 compared to Buphenyl, respectively. Mean PAGN AUC and urinary excretion of PAGN over 24 hours were both ~20% lower after HPN-100 than after Buphenyl. The urinary excretion of PAA and PBA was about three orders of magnitude lower than that of PAGN, signifying that most of the PAA binds to glutamine prior to excretion.

Single and multiple dose PK studies in healthy adults demonstrated that the half-life of PBA is short (1.9 hours). There is no accumulation of PBA in plasma in healthy subjects. PAA and PAGN levels increase initially and then reach a plateau after the first 1–3 days of multiple dosing, indicating that steady state is reached by day 3.

After twice daily dosing for 7 days in healthy adults, the systemic exposure to PBA and PAGN increased by 40-50% compared to an approximate 300% increase in the PAA exposure, possibly indicating that the rate limiting step is the conversion of PAA to PAGN.

In the pivotal study, the peak concentrations of PBA after HPN-100 were delayed compared to NaPBA (8 hr after dose compared to 3 hr after dose) and never got as high. Mean systemic exposure (AUC₀₋₂₄) of plasma PBA was numerically lower on HPN-100 compared with NaPBA treatment reflecting lower overall exposure (~20% lower). Also, there was lower fluctuation between C_{max} (51.9 µg/mL) and C_{min} (1.44 µg/mL) on HPN-100 as compared to NaPBA (C_{max} 80.9 µg/mL and C_{min} 0.0905 µg/mL). The PAA kinetics also peaked later for HPN-100, the peak wasn't as high, there was a lower AUC₀₋₂₄, and there was a smaller difference between C_{max} and C_{min}. It is important to note that these were exploratory findings and furthermore, none of the differences were statistically significant. However, the lower PAA levels (AUC₀₋₂₄) during HPN-100 dosing compared to Buphenyl dosing is reassuring from a safety perspective. See Figure 3.

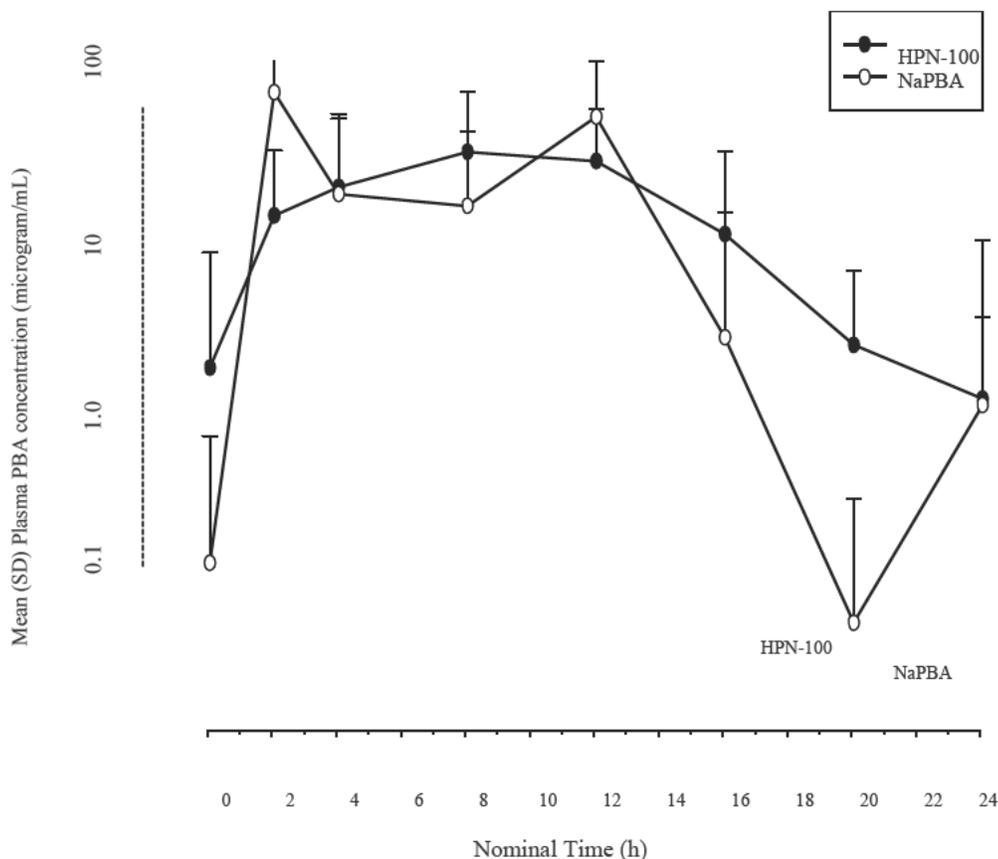


Figure 3: Mean (\pm SD) Plasma Concentrations of PBA versus Time Following Multiple Oral TID administration of NaPBA and HPN-100 for 14 Days – Semi-Log Plot (ITT Population)

Source: Study Report HPN-100-006, p. 84

Distribution/ Protein Binding

In vitro, the extent of plasma protein binding for ^{14}C - labeled metabolites was measured using ultrafiltration. The protein binding was moderate to high for PBA (80.6% to 98.0% over the concentration range 1 – 250 $\mu\text{g/mL}$), low to moderate for PAA (37.1% to 65.6% over the concentration range 5 – 500 $\mu\text{g/mL}$) and low for PAGN and no concentration effects noted (7.3-12 % over the concentration range 1-250 $\mu\text{g/mL}$). The clinical pharmacology review provides more detail regarding volume of distribution of Ravicti and its metabolites.

Drug Metabolism and Excretion

Upon oral administration, hydrolysis of HPN-100 releases PBA which is absorbed into the enterocytes. PBA is converted by β -oxidation to PAA which conjugates with glutamine in the liver and kidneys to form PAGN via acetylation by phenylacetyl-CoA: L-glutamine-N-acetyltransferase. PAGN is subsequently eliminated by the kidneys via glomerular filtration and tubular secretion.

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While total PAGN excretion was essentially the same for both drugs, significantly less PAGN was excreted in urine during the 12–24 h (overnight collection) period than during the 0–12 h (daytime collection) period following NaPBA treatment, whereas after treatment with HPN-100, U-PAGN was more evenly distributed over 24 h (32.0% versus 36.8%, respectively).

Metabolism and excretion appeared to be dose proportional in the healthy volunteers, but little could be said regarding the maintenance of dose proportionality for doses above 6 mL TID. The dose proportionality of metabolism and excretion might vary by underlying disease, glutamine levels, etc.

Intrinsic Factors that might affect PK

Age: Simulations suggest that PAA C_{max} would be below 500 µg/mL in most pediatric patients above two years of age at the highest proposed dose of HPN-100 and it would be comparable between Buphenyl and HPN-100 treatments. There were insufficient data to simulate what would occur in patients under 2 years of age.

Ravicti was not studied in neonates younger than 2 months, a concern because of inadequate pancreatic exocrine function in many patients this age. While there is no experience with HPN-100 in neonates, if intestinal hydrolysis of HPN-100 is deficient because of immature pancreatic exocrine function, decreased PBA formation and absorption might lead to the inadequate control of blood ammonia. For this reason, Ravicti should not be used in neonates until further efficacy data is obtained.

There were 6 patients above 50. The oldest patient was 75 years old.

Gender: Gender-based effects were noted for all metabolites, with females having higher plasma concentrations, in general, compared to males. The C_{max} of PAA was ~51% higher in females in the 4 mL TID group and ~120% higher in the 6 mL TID group, with less PAGN excretion in urine (14% lower in females than males). A similar gender effect was also noted for Buphenyl and is in the Buphenyl labeling. It should be noted that these were fixed doses so it is possible that the differences in C_{max} levels had more to do with differences between men and women in body weight/BSA.

Renal impairment: The effect of renal impairment on the pharmacokinetics of Ravicti and its metabolites was not studied. Since the pathway of elimination of Ravicti is through the urine, via its metabolite, PAA or U-PAGN, renal insufficiency or drugs that interfere with renal function or secretion could conceivably create PAA increases and toxicity. There are no data on Ravicti safety and efficacy in patients with renal failure. This will be stated in the label in the pharmacokinetics section.

Hepatic impairment: Patients with advanced hepatic disease had elevated PAA/PAGN ratios and are therefore at risk of developing PAA toxicity. The review team agreed that there should be a warning for this subpopulation and instructions about a lower starting dose.

UCD subtype: There is great variation among patients within UCD subtypes regarding dose required, particularly within the OTC adult subtype. See Table 1. A few disorders were

only represented by 1 patient in the whole development program, so a comprehensive analysis of the dosing as well as other effects of treatment in these subgroups is not possible. The majority of patients in the pivotal trial, HPN-100-006 had OTC deficiency which in most series usually accounts for 50% of UCD patients. In adults, though, it's probably higher because most are women and have milder cases in general and thus are more likely to survive to adulthood without getting a liver transplant. Patients affected by ASL, ARG and HHH are less likely in general to be on phenylbutyrate because they are more easily controlled with diet and amino acid supplementation. CPS I and ASS deficiencies are relatively rare and severe, so most patients are transplanted by adulthood or have died.³⁶

Table 1: Mean total daily dose (g/m²; min, max) by UCD subtype

Study	HPN-100-012	HPN-100-005	UP-1204-003	HPN-100-006
Age	> 28 day, < 6 yr	> 6 yr, < 12 yr	Adult	Adult
Subtype				
OTC	8.78 (6.9-11.5) (n=3)	10 (6.9-14.4) (n=9)	7 (4.9-9.9) (n=8)	7.6 (0.7-15.4) (n=40)
ASL	6.84 (1.5-10.1) (n=8)	6.7 (n=1)		
ASS	11.6 (9.3-14.1) (n=3)	11.3 (n=1)	8.2 (n=1)	5.7 (2.6-7.9) (n=3)
ARG	7.17 (n=1)			
CPS I				10.9 (n=1)
HHH			6.14 (n=1)	

Source: Clinical Pharmacology Review, table 29.

Extrinsic Factors that might affect PK:

Food effects: Other amino acid preparations and dietary factors play a role in efficacy of pharmacotherapy in UCDs. Often patients are treated with arginine and citrulline depending on the UCD. Protein restriction depends on the age of the patient. If the patient is growing, more protein is needed to prevent growth retardation. Food effects were not formally evaluated during this development program. HPN-100 was administered with meals in all clinical studies in UCD patients and this is the way it needs to be taken to effectively control the postprandial increase in blood ammonia. The lack of a typical food effect study was not considered to be an important issue by the Clinical Pharmacology team.

Drug-Drug interactions:

HPN-100 is most probably hydrolyzed in the gut lumen before any intestinal absorption. So, drug interaction studies were more focused on the metabolites of HPN-100. *In vitro* studies using human hepatocytes were conducted to evaluate the potential for PBA and PAA to induce and to inhibit CYP enzymes. Results from these studies showed that PBA and PAA did not pose any significant potential ($\geq 40\%$ activity) for induction of CYP1A2 or CYP3A4/5.

³⁶ Discussion with M. Tuchman

• Cross Discipline Team Leader Review • Melanie Blank, MD, DGIEP • NDA 203284 • Standard review for Ravicti™ (glycerol phenylbutyrate) liquid for oral administration • Class: Nitrogen Binding

In vitro studies using human liver microsomes showed Ravicti may slightly inhibit CYP2C9 and CYP3A4/5. The principle metabolite PBA caused >60% reversible *in vitro* inhibition of cytochrome P450 isoenzymes CYP2C9, CYP2D6 and CYP3A4/5 (testosterone 6β-hydroxylase activity). The PAA metabolite caused reversible *in vitro* inhibition ranging from 37% to ≥ 60% to CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The clinical significance of these findings is uncertain as they occurred at concentrations 20-fold higher than the C_{max} achieved clinically. The Clinical Pharmacology review stated some concern about the potential for drug-drug interactions because of the variability of Ravicti dosing. The Clinical Pharmacology review suggested language in the label about the CYP *in vitro* inhibition and the review team agrees. The Clinical Pharmacology team has requested a PMR to investigate further the potential for drug-drug interactions based on CYP enzyme inhibition. Hyperion has agreed to conduct this study as a PMR.

HYP-100 is not a substrate of CYP enzymes and therefore, it is not a competitive inhibitor.

The interaction study with p-gp was not studied for HPN-100 and its major metabolites. The Clinical Pharmacology reviewer did not recommend a p-gp interaction study.

PHARMACODYNAMICS

Assays of NH₃ and metabolites

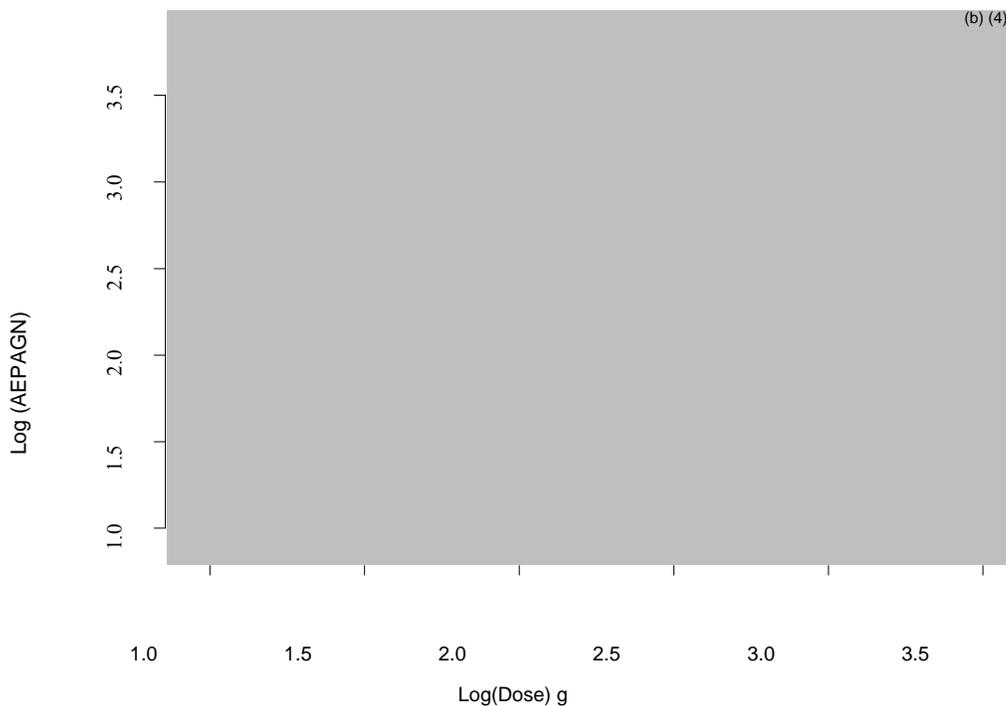
In HPN-100-006, eleven different assay kits were used for blood ammonia measurements. Each lab was a CLIA-approved laboratory. Because of the importance of rapid analysis of blood ammonia, blood ammonia levels were measured at each study site instead of a central laboratory using commercially available assay kits. The ammonia values for a given patient were measured at the same laboratory after Buphenyl or Ravicti treatment to mitigate inter-laboratory and/or inter-site differences in methodology. Blood ammonia was measured by colorimetric method or enzymatic method for 28 patients and 17 patients, respectively. When mean AUC_{NH₃ 0-24} was compared by the assay principle, mean ammonia AUC differed by 2-2.5 fold; greater with enzymatic method than colorimetric method. Nevertheless, the difference in the assay principle did not change the overall conclusion as the upper limit of 90% CI ratio was lower than 1.25. Because of the above findings, the Clinical Pharmacology review concluded that there were no major concerns with the variety of ammonia assays used in the pivotal trial. It is a deficiency in the study that a central laboratory was not used, but this deficiency was probably not avoidable since there were so many centers and to replace their testing methods would probably have been prohibitively expensive. It was finally decided that presenting the non-normalized data in the label would add more to the confusion than presenting the normalized data. Therefore, the data in the label will be normalized ammonia data with an explanation for how normalization was accomplished.

Dose Response

There was not a strong dose-response relationship found between HPN-100 (or NaPBA) and ammonia levels. This is most likely because the patients were already in a steady state of

ammonia production/ excretion at the time the study began and because each patient's dose of nitrogen-binding agents is dependent upon 3 main variables; the type of UCD deficiency, the protein content of their diet and their catabolic/anabolic state. Therefore, there would be expected to be a good deal of interpatient variability and even inpatient variability when doses are kept constant as they were in the controlled studies.

Despite the absence of a strong dose-response relationship between drug dose and ammonia level, among all 65 UCD patients who completed UP 1204- 003, HPN-100-005 SO and HPN-100-006, U-PAGN₀₋₂₄ was linearly related to PBA administered (Figure 3). This supports the theory that the absence of a dose response relationship with ammonia level is more likely a product of the variability in UCD deficiency, diet and catabolic/anabolic states among patients.



AE = amount excreted;

Figure 4: Relationship Between PAGN Excretion in Urine and Dose of PBA After Doses of HPN-100 and NaPBA in Adult and Pediatric Patients with UCDs— Clinical Studies UP 1204-003, HPN-100-006, and HPN-100-005

Source, Clinical Overview, p. 65

Rationale for the proposed daily dose range

The label as proposed by the applicant suggested a dose range i.e. 4.5-11.2 mL/m² (5-12.4 g/m²). This proposed dose range is based on the range of maintenance PBA dosages on which the UCD patients entered the study. The dose range proposed by Hyperion for Ravicti starts at the 25th% quartile of the dosages that patients received in the pivotal trial and ends with the

same maximum dose of PBA that is advised in the Buphenyl label. The proposed lower end of the dose range is about 50% lower than the lower end of approved Buphenyl dose i.e. 9.9 g/m² for patients > 20 kg. In reality, some patients may need less. The trial demonstrated that 25% of the patients did receive lower doses than the proposed range. Patients should not get more than they need because of the toxicities of PBA and PAA. Most of the patients who enrolled in the trial were on lower doses of Buphenyl than the Buphenyl label recommends. The reason for this is not known. The likeliest reason is that these are stable patients who are adults and have not had severe disease. Perhaps because many had partial, not complete defects or enzyme defects that often don't require PBA treatment, the patients enrolled in this study required less medication than the average patient with UCD.

The original applicant-proposed starting dose for Ravicti was (b) (4)/day. This equates to (b) (4)/day of Buphenyl which is under the dosing recommendation for Buphenyl (9.9 -13 g/m²/day).

There were only 6 patients in the development program who started Ravicti without having already been on a stable dose of NaPBA. Two of these patients could not tolerate Ravicti. Patient 07-7714 was treatment naïve when she entered study HPN-100-007, and was started at a dose of 17.4 mL/day. Her dose was reduced by 50% pursuant to neurological TEAEs. She eventually withdrew consent. Her PAA levels were all within the range thought to be tolerable and nontoxic. Patient 18-7624 also had a dose reduction due to vomiting. No PAA levels were obtained for her.

After a discussion with the applicant about structuring the Dosage and Administration section to cover three main situations:

- Switching from NaPBA
- Starting a patient on Ravicti who has little endogenous urea cycle activity
- A patient who has a mild case of UCD.

The current proposal is to provide a conversion equation between NaPBA and Ravicti in the label when patients are being switched from NaPBA to Ravicti. If the patient is treatment naïve to both products and dosing is required that covers most/ all dietary protein that is not needed for anabolic functions of the body, the advice is to calculate the protein requirement and determine dose accordingly using a formula that equates dietary protein requirement to Ravicti dosage. If a patient has a milder form of UCD, the suggestion in the label is currently to start the dose at 4.5 mL/m²/day. This appears to be the best suggestion to date.

The dosing issue is important because UCDs can be life-threatening and underdosing could be fatal. On the other hand, overdosing can cause PAA toxicity as well as nitrogen depletion which can result in symptoms of protein malnutrition (often presenting as skin and hair abnormalities but could have growth consequences).³⁷ A PMR for dosing treatment naïve patients of all ages was proposed to the applicant and they agreed.

Children younger than 6 years old enrolled into Study HPN-100-012 on lower doses of Buphenyl than what is recommended in the Buphenyl label. This also may be a reflection of

³⁷ Conversation with Dr. M. Tuchman

milder disease or better disease control because of diet. Most patients with severe disease will probably have had liver transplant by age 5. Similar to what was seen in adult UCD patients, in pediatric patients aged <6 years old, the observed mean dose was 331 mg/kg and lower than the lower end of the Buphenyl dose range i.e. 450 mg/kg for patients < 20 kg. Dosing treatment-naïve patients with Ravicti will be studied in a PMR study in this younger patient population (under 2 years of age). For the children under 2 years of age, no dose recommendations can be made because of the paucity of data in this age cohort.

The applicant proposes

(b) (4)

PAA levels and safety

There are concerns about the toxicity of PBA/ PAA. The pharmacology/ toxicology findings of neurotoxicity (see previous Pharmacology/Toxicology section) in addition to clinical evidence of neurotoxicity: a literature report highlighting neurotoxicity findings in patients treated with NaPBA given intravenously³⁸, and a case series of coma and death after overdose of IV PAA and Benzoate in young children³⁹ create cause for concern about neurotoxicity from HPN-100. In the Thibault study, PAA levels $\geq 500 \mu$ were associated with somnolence, emesis and lethargy in patients with cancer who received IV PAA. More severe toxicity (confusion and psychomotor depression) occurred in patients with mean peak PAA level of 682 μ g/mL.⁴⁰ These adverse reactions were reversible when the PAA infusion was discontinued. In an article by Simell et al⁴¹ the safe upper PAA concentration limit was calculated to be 476 μ g/mL.

PAA toxicity was explored in the Clinical Pharmacology review using PK/PD data from this NDA. The only study that showed a dose-relationship between PAA and toxicity was the thorough QTc study done in healthy subjects. There were several dosage groups of varying

³⁸ Thibault A et al, (1995) Phase I study of phenylacetate administered twice daily to patients with cancer. *Cancer* 75:2932-8

³⁹ Praphanpho et al, (2000) Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonemia, *J Inher Metab Dis* 23: 129-36

⁴⁰ Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. *Cancer* 1995;75:2932-8.

⁴¹ Simell O, et al. Waste Nitrogen Excretion via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance. *Pediatr Res.* 20: 1117-1121, 1986

sizes in the QTc study. There were only 4 subjects in the 12 mL TID group and 12 subjects in the 9 mL TID group compared to much larger numbers in the 6 mL TID group (n=75), in the 4 mL TID group (n=68), and in the placebo TID group (n=84), which would normally make it difficult to assess dose relationships. Nevertheless, in Table 2, the direct relationship between dose and AEs and discontinuations is demonstrated in healthy subjects. As for the types of neurological or psychological AEs that were dose related in frequency, they were headaches, dizziness, somnolence, fatigue, visual impairment, presyncope, sleep disorder, depressed mood, visual disorder, tinnitus, hallucination and euphoria. The only two neurological events classified as severe occurred in the 9 mL TID group (headache and dizziness). The likelihood of have 2 or 3 neurologically related AEs in the same patient was also dose related. There were no neurological SAEs in the QTc study. The relationship between PAA concentration and neurological AEs is modeled in Figure 5. While the healthy volunteers enrolled in this study are not reflective of the population who will be using this drug, the PAA/ AE relationship derived from their data may be more reliable for teasing out the toxicities of HPN-100 because enrolled patients with UCDs may have developed tolerance, were innately more tolerant (those that were not tolerant would have previously failed trials of NaPBA), or have many of the same symptoms as part of their underlying disorder and therefore not be able to recognize PAA toxicity symptoms. Another confounding aspect of the analysis of AEs and PAA levels in UCD patients is that PAA levels were not drawn at the time of AEs. PAA levels vary considerably relative to the interval between time of dosing and it is not possible to draw conclusions about the relationship between PAA levels and AEs unless the PAA level is drawn at its peak level in the hours before the AE. Therefore, in the UCD population, defining the relationship between drug level/ exposure and AEs may not be straight forward. In Figure 6 one can see the lack of a demonstrable relationship between PAA levels and AEs in the UCD population. However, one can not be sure that a relationship does not exist because the protocol did not include frequent PAA monitoring or PAA monitoring at time of AEs.

Table 2: Treatment-emergent adverse events (TEAES)* by dose in healthy subjects

	Placebo	4 ml ¹ TID	6 ml ² TID	9 ml TID	12 ml TID
N exposed	84	68	75	12	4
Discontinued due to AE (%)	4 (4.8)	3 (4.4)	7 (9.3)	4 (33.3)	1 (25)
One or more neurological AE	8 (9.5)	18 (26.5)	35 (46.6)	11 (91.7)	3 (75)
One or more GI AEs	9 (10.7)	8 (11.8)	24 (32)	9 (75)	4 (100)

*A treatment-emergent adverse event is an AE that begins (or a preexisting AE that worsens) after receiving the study medication through 7 days after the last dose of study medication.

¹Similar to the proposed starting daily dose i.e. (b)(4)/day for patients with BSA of 1.7 m²

²Similar to the proposed upper limit of the daily dose i.e. 17.5 ml/day

Source: Dr. Kim's Pharmacology/ toxicology review

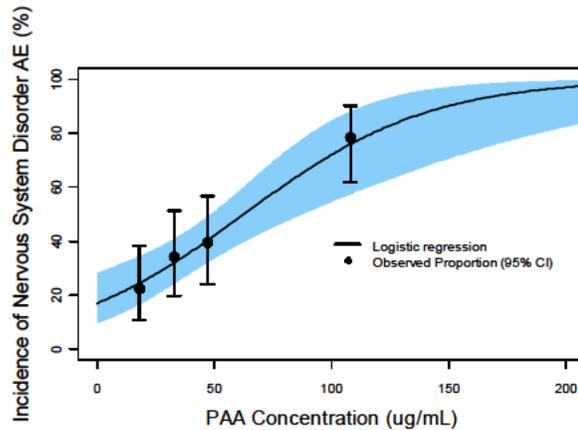


Figure 5: Relationship between PAA C_{max} (ug/mL) and Incidence of Nervous System Adverse Events in Healthy Volunteers

Source: Clinical Pharmacology Review by Dr. Kim and Dr. Krudys

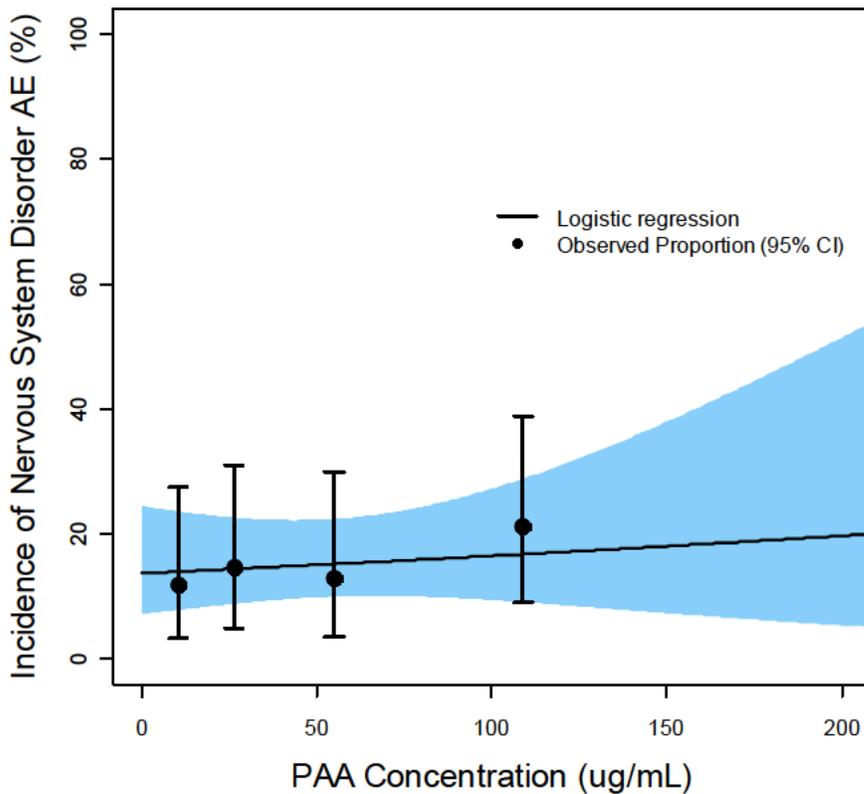


Figure 6: Lack of Relationship between PAA C_{max} (ug/mL) and Incidence of Nervous System Adverse Events in UCD Patients

Source: Clinical Pharmacology Review by Dr. Kim and Dr. Krudys

As the Clinical Pharmacology review pointed out, for a relationship between PAA levels and nervous system disorders to be observed, one might need to study individual dose titration over a range of doses in a treatment-naïve individual. Another approach would be a dose-

ranging study in patients who are treatment-naïve where PAA levels would be drawn at peak concentration. The HPN-100 studies only included 6 treatment-naïve patients. As stated earlier in this review, 2 of the 6 treatment-naïve patients were discontinued for symptoms that were probably related to drug intolerance. One of the patients had neurological symptoms and the other had vomiting. PAA levels were not elevated at the time they were measured, but it is unclear when they were measured relative to dosing or AE.

It is reassuring to note, as shown in Figure 7 that there is a trend of lower PAA C_{max} for UCD patients when they are dosed on HPN-100 compared to Buphenyl at equivalent doses at median or higher doses. The reliability of the results comparing PAA levels to neurological AEs is high for the QT study, because PAA levels were drawn frequently and at appropriate times relative to dosing. Some subjects had neurological AEs at low levels at PAA, suggesting that some of these events may have been related to elevated ammonia levels, or that the degree of capture of elevated PAA levels was poor.

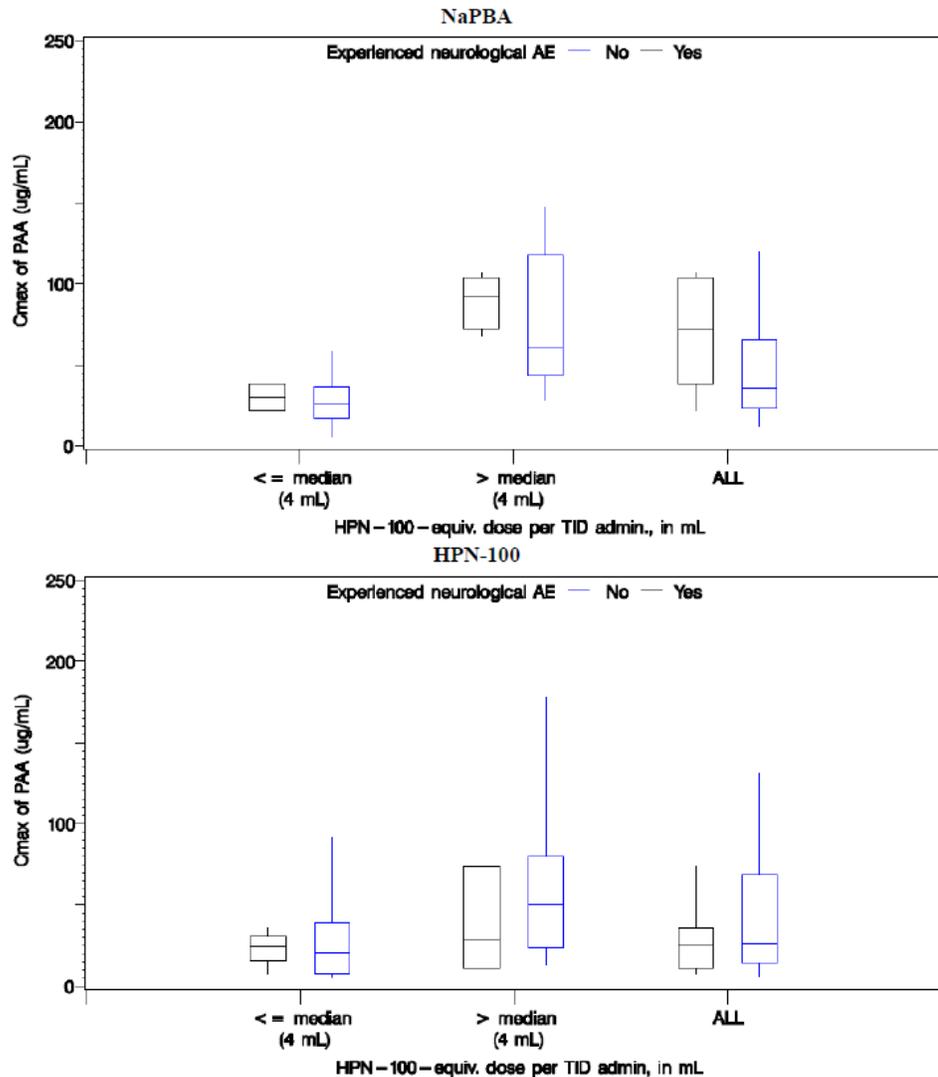


Figure 7: PAA C_{max} by Neurological Adverse Event Status in UCD Patients

Source: Summary of Clinical Safety, Figure 2.7.4-3, Page 95

Dr. Snow pointed out in her Clinical review that the mean PAA levels during the trials were in the acceptable range relative to what was observed as causing severe toxicity in the Thibault study⁴² and no patients other than the children under 2 years of age had elevated PAA levels in the range of concern ($\geq 500 \mu\text{g/mL}$). During Study HPN-100-012 (the study that enrolled children 2 months to 5 years of age), there was one 2 month old infant who had a peak PAA level of $530 \mu\text{g/mL}$ when receiving NaPBA. There was a one year old who had a peak PAA level of $480 \mu\text{g/mL}$ on Ravicti.

Dr. Snow did an analysis of UCD patients \leq five years of age to explore the relationship between AEs and PAA Cmax. See Table 3. There was no obvious relationship demonstrated. Unfortunately, there were several missing values so one cannot be sure that there weren't other significant elevations in PAA. Additionally, it is unknown what the PAA levels were at the times of the AE. For these two reasons, lack of correlation between AEs and PAA levels found in Dr. Snow's analysis could possibly be misleading. Dr. Snow also pointed out that the ammonia levels at the time of the AEs were not evaluated. For the four patients under age 6 who had no AEs during the 10-day trial, the highest PAA level was $206 \mu\text{g/mL}$. This occurred on day 10 of Ravicti. Similar PAA levels were noted on day 1 when patients were on Buphenyl.

⁴² Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. *Cancer* 1995;75:2932-8.

Table 3: Adverse Event by patient in HPN-100-012 SO 10-day trial (enrolled only patients ≤5 years of age) while on HPN-100 and corresponding Cmax during the trial. Only patients with AEs are included in this table.

Patient	Age	Adverse Event while on Ravicti	CTCAE Grade	Action taken	PAA Cmax Ravicti (µg/mL)	PAA Cmax Buphenyl (µg/mL) before Switch over to Ravicti
05-1210	1 year	Vomiting	1	Dose not changed	480	286
05-1213	3 years	Respiratory Infect.	1	Dose not changed	7.43	18.5
10-1214	2 years	Heart Murmur	1	Dose not changed	3.48	Below LOQ
11-1201	5 years	Abd.Discomfort, nausea	2	Dose not changed	72.9	69.6
16-1215	1 year	Papule	1	Dose not changed	99.3	76.8
01-1212	5 years	Vomiting x 4	1	Dose not changed	52.4	57.9
04-1202	3 years	Lymphadenopathy	1	Dose not changed	93.3	41.7
05-1209	2 months	Flatulence/ patient later (in the extension study) had respiratory infection, bilious vomiting and then grade 3 failure to feed (PAA levels not known at the time of this event, but ammonia was 116 mcg/dL)	1	Dose not changed	Below LOQ	530

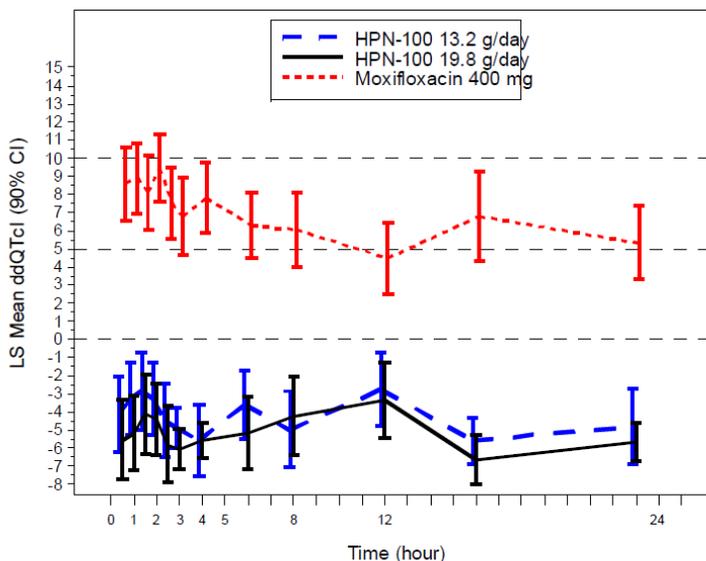
[Ref: HPN100-012 Switch over Analysis, Listing 16.2.7.1, p.2-3.]
Source: Nancy Snow, MD. Primary Clinical Review

PAA toxicity is a particular concern for patients 2 months to < 2 years of age. There were only 4 patients studied; the highest PAA levels in the development program were observed in two of these 4 patients and symptoms of lethargy, dizziness, impaired sensorium, etc. would be hard, if not impossible to detect. Patient 05-1209 who was a black African American female with AS deficiency, had elevated PAA levels in the first 10 days of treatment. However, she had elevated ammonia levels when she had her Grade 3 AE of failure to feed associated with an upper respiratory infection and bilious vomiting. Her PAA levels were not tested at the time of her AEs.

The uncertainty around the PAA levels and relationships to AEs in the young children has prompted the review team to advise the applicant to commit to a PMR to study the safety and efficacy of HPN-100 in the subpopulation of patients between 2 months and 2 years of age. PAA levels will be monitored as well on a regular basis and at the time of AEs. It would be prudent to study treatment-naïve patients and perform an actively controlled double blind study with NaPBA as the active comparator so that comparisons can be made between the PAA levels and safety profiles of the two drugs.

- Inconclusive TQT study

The substantial difference in the ddQTcI-time profile between moxifloxacin and HPN-100 seen in the TQT study as shown in Figure 8 would usually be convincing of an absence of a HPN-100 QT prolonging effect.



(Note: CIs are all unadjusted including moxifloxacin)

Figure 8: QT study results (from applicant)

However, the time profile for moxifloxacin, the active control, was not consistent with the expected moxifloxacin time course, making the TQT study inconclusive. In this light, it was important to search for evidence of QT prolongation and/or arrhythmia in the clinical studies. There were two AEs that require special consideration: **Patient 04-5041** in study HPN-100-005SE (6–11 years) had an AE of Grade 2 abnormal ECG (borderline prolonged QT interval) reported at the Month 12 visit, which was considered clinically significant and possibly related to study drug. The AE resolved in 45 days after the patient completed the study and switched back to sodium phenylbutyrate. Follow-up with cardiology was recommended. **Patient 12-7612** in HPN-100-007 had ventricular fibrillation which occurred during a liver transplantation that occurred the day after stopping HPN-100. The level of metabolites was probably very low in the patient who had the transplantation because it was done on the day following Ravicti discontinuation.

Aside from these events, there were no overall concerns regarding EKG changes in the clinical trials. The adverse events of prolonged QT interval and ventricular fibrillation may or may not be related HPN-100. It is hard to judge. For this reason, OSE was asked to query the AERS database for a signal of arrhythmia for Buphenyl. There was also a patient in one of the hepatic impairment studies who had an increase in QTc > 60 msec over the patient's morning value.

Dr. Thang, the OSE reviewer, found 8 FAERS reports of ECG changes, sudden death or hyperammonemic crises resulting in death in patients on Buphenyl which were probably not related to QT effects. There was one report of a 9 year old female with OTC deficiency receiving Buphenyl who had ventricular tachycardia followed by death while undergoing dialysis. The patient also had a potassium level of 2.8 meq/L at the time of death, which alone could have accounted for the arrhythmia.

It is possible that the borderline QT prolongation and ventricular arrhythmia may be unrelated to HPN-100 seen in the Ravicti development program. However, in the setting of an inconclusive TQT study and a small patient database, there remains some concern. The conclusion of the QT-IRT review was that, “We do not believe assay sensitivity had been successfully demonstrated in this study (...). Therefore, QT-IRT suggests a PMR for further evaluation of the cardiovascular safety for the study drug.” If this were not an orphan product, it would be advisable to compel the applicant to repeat the TQT study as a PMR. However, the evidence that there is a true QT signal is not compelling. There was only one patient in the clinical trials who was documented to have QT prolongation and it is not clear from the case report if other factors may have contributed to this finding. Furthermore, the patient did not develop a documented arrhythmia despite staying on HPN-100.

While it would be ideal to have the QT study repeated because of the lack of assay sensitivity, the QT results of the Ravicti did not reveal an upswing and the data were not highly variable. For these reasons, it is considered unlikely that Ravicti will increase the QT interval by ≥ 10 ms, even in the absence of assay sensitivity. For this reason, it is not necessary to repeat the QT study for approval.

The review team in consultation with the QT IRT team decided that it would be acceptable to add labeling that informs prescribers that the study did not have enough assay sensitivity to rule out QT interval prolongation of 10 msec:

6. Clinical Microbiology

Not applicable for this orally administered agent.

7. Clinical/Statistical- Efficacy

The indication sought by the applicant is: “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).”

Ravicti is a nitrogen binder and its proposed use is for adjunctive treatment (in addition to dietary restrictions and amino acid supplementation) in the chronic management of all urea cycle disorders (UCDs). NaPBA (Buphenyl), which has the same active moiety (PBA) as Ravicti, is the only available oral therapy marketed for UCDs. Its indication differs from the proposed Ravicti indication [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).]: the Buphenyl label specifies in its INDICATIONS AND USAGE section that, “BUPHENYL® is indicated 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). 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.”

The first sentence of the Buphenyl indication limits the drug unqualified to a subgroup of UCD enzyme deficiencies (carbamyl phosphate synthetase, ornithine transcarbamylase, and argininosuccinic acid synthetase). These are the proximal enzyme disorders and typically have the worst presentation and are usually refractory to dietary management and amino acid supplementation. However, the Buphenyl also makes it clear that it is also indicated for any enzyme disorder that presents within the first 28 days of life, or in any UCD patients who have hyperammonemic crisis. It is used in practice for all disorders even in patients with NAGS deficiency (the Carbaglu®, carglumic Acid label Dosage and Administration section states that, “Concomitant administration of other ammonia lowering therapies is recommended.”)⁴³ Buphenyl has the same active moiety as Ravicti. Therefore, there is no reason to suspect that Ravicti should not be expected to work in any patient who is in need of nitrogen binding, as long as the patient can absorb the drug.

The main reason that Ravicti and Buphenyl are not appropriate as lone therapy for patients with NAGS deficiency is that there is an approved enzyme replacement therapy for NAGS deficiency, Carbaglu® (carglumic acid), which is indicated for this particular UCD.

The indication for Ravicti should include all UCD disorders that cannot be managed by dietary protein restriction, or amino acid supplementation or Carbaglu alone. Because there were no patients with NAGS deficiency in the development program, it is reasonable to state the safety and efficacy in this population is unknown.

⁴³ Carbaglu label

To support the application, there is one main efficacy trial; the phase 3 pivotal trial, HPN-100-006 in adults with UCDs. There is supportive evidence from the phase 2 open-label uncontrolled switch over trial, HPN-100-005 SO conducted in children with UCDs ages 6-17 and the phase 2 switch over trial, HPN-100-012 SO, conducted in children under 6 with UCDs. There were two completed extension trials: HPN-100-007, the extension trial for HPN-100-006 which allowed enrollment of patients age 6-17 as well as adults who had not been enrolled in HPN-100-006) and HPN-100-005 SE, the 12-month open label extension trial for HPN-100-005 SO. These extension trials provided support for long-term efficacy of Ravicti because ammonia was well controlled in most patients throughout the extension phases, a finding that would not be expected in the absence of effective nitrogen binding therapy. None of these trials, however, were controlled or had prespecified statistical endpoints, making them less reliable than the pivotal trial in adults.

There was also an extension trial for the 2 month – 5 year old switch-over trial (HPN-100-012SO). It was called HPN-100-012SE. While not controlled and with no prespecified statistical endpoints, and not completed, it also provided some supportive evidence of efficacy in that ammonia levels were generally well controlled.

The supportive data were not reviewed by the statistical reviewer. At best, they can be seen as supportive. Most of the patients had been started on Buphenyl prior to enrollment. This means that they had one of the three most serious UCD enzyme defects, had presented in the first month of life with hyperammonemia, or had hyperammonemic crisis with encephalopathy at any time in their lives. Patients like this would not be expected to maintain ammonia control over a 12-month period without effective therapy. For this reason, the open-label studies can be considered to be historically controlled and therefore, supportive evidence of efficacy.

Regulatory Background and selection of primary endpoint:

April 10, 2007: HPN-100 IND established

May 5, 2006: Orphan drug designation granted

June 30, 2009: SPA agreement for phase 3 protocol HPN-100-006

October 12, 2009: HPN-100-006 started

September 9, 2010: HPN-100-006 completed

September 23, 2010: Statistical analysis plan for HPN-100-006 finalized

September 30, 2010: Database hardlock

October 4, 2010: Fast-track designation granted for HPN-100

October 7, 2010: Data unblinding

December 23, 2011: submission of NDA, including a REMS which the FDA instructed

Hyperion to submit unless it was planning on submitting data on patients between 29 days and 5 years of age

August 23, 2012: Hyperion Therapeutics, Inc. solicited major amendment which extended the user fee goal date to January 23, 2012. The new submission included the clinical trials in patients between 2 months and 5 years of age which satisfied the requirement for avoiding the REMS.

Elevated blood ammonia is the common signature feature of UCDs. Control of blood ammonia is a primary objective of clinical management, and blood ammonia levels have been shown to correlate with clinical outcome (Batshaw, 1984;⁴⁴ Enns, 2007;⁴⁵ Logan, 1984.)⁴⁶ Therefore, in consultation with the FDA in the context of a Special Protocol Assessment (SPA), venous blood ammonia, assessed as AUC₀₋₂₄ at the end of each treatment period (Days 14 and 28), i.e., during steady-state dosing with HPN-100 or NaPBA, was selected as the primary efficacy endpoint in the pivotal efficacy study, HPN-100-006. Venous blood ammonia levels have been used as primary endpoints for other UCD products. Both NaPBA (Buphenyl) and carglumic acid (Carbaglu) for the treatment of NAGS deficiency were approved on the basis of treatment effect on ammonia levels. For the approval of Buphenyl, however, plasma ammonia glutamine level (an endogenous nitrogen carrier), was the primary measure of efficacy. Both glutamine and ammonia levels are appropriate endpoints because they both carry nitrogen and correlate with one another. Ammonia also circulates in the body as free ammonia or within glutamine which functions as a temporary “repository” for ammonia. Consequently, in a urea cycle defect not only does free ammonia rise (hyperammonemia) but glutamine is also elevated. Alanine (Ala) is another amino acid that accumulates as a result of hyperammonemia due to a urea cycle defect. These two amino acid elevations (glutamine, alanine) may precede hyperammonemia and the onset of clinical symptoms and can serve as useful biochemical markers of decompensation in a patient with a urea cycle defect.^{47,48} PAGN is excreted relatively rapidly in the urine. And since PAA binds to ammonia to make PAGN, it would be expected that urine PAGN levels would also reflect ammonia control. In the pivotal trial, urine PAGN correlated extremely well with serum ammonia. However, if a patient had renal failure, urine PAGN might go down despite high ammonia levels and in hepatic failure, urine PAGN might go down despite poor ammonia control. Therefore, serum PAGN would not be an ideal marker of efficacy in certain circumstances.

Nitrogen binders (drugs that allow elimination of ammonia through the alternative pathways) are effective for the chronic management of UCDs when properly dosed. (See pp. 14-15). Nevertheless, patients must be compliant with NaPBA and diet in order to thrive. Even with compliance, intercurrent infection or other stressful occurrences, and catabolic states can induce hyperammonemia and life-threatening illness. A randomized, active controlled (with NaPBA), cross-over, noninferiority-design trial to evaluate the safety and effectiveness of HPN-100 was agreed upon by the FDA in the form of an SPA and this decision was appropriate.

⁴⁴ Batshaw ML. Hyperammonemia. *Curr Probl Pediatr* 1984;14(11):1-69

⁴⁵ Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *New Engl J Med*. 2007; 356:2282-92.

⁴⁶ Logan WJ. Neonatal hyperammonemic encephalopathy. In: Sarnat HB, editor. *Topics in neonatal neurology* 1984. p. 137-57.

⁴⁷ The urea cycle disorders conference group (2001). Consensus statement from a conference for the management of patients with urea cycle disorders. *Supplement to the Journal of Pediatrics*. Vol. 138 (1).

⁴⁸ Saudubray JM, et al, (2012), *Inborn Metabolic Diseases: chapter 20, Disorders of the Urea Cycle and Related Enzymes*. pp. 298-310.

The timing of the ammonia measurements for measurement of AUC of blood ammonia was discussed and agreed upon with FDA at the End of Phase 2 meeting (End of Phase 2 Meeting Minutes, January 14, 2009), and the FDA agreed to the overall analytical approach to assessing efficacy based on ammonia AUC₀₋₂₄ in a SPA agreement letter (FDA Agreement Letter dated June 30, 2009). In the Phase 2 supportive efficacy studies, blood ammonia AUC₀₋₂₄ on Day 7 and Day 14 was evaluated by post hoc efficacy analysis in adult UCD patients in UP 1204-003 and was pre-specified as an efficacy endpoint in uncontrolled studies in pediatric UCD patients (Study HPN-100-005 and Study HPN-100-012).

Description of the Efficacy trials

HPN-100-006 is the pivotal efficacy trial. It was a double-blind, randomized, active-controlled, cross over study in subjects with urea cycle disorders (UCD) who were being treated with NaPBA (sodium phenylbutyrate) for their UCD. Subjects were randomly assigned to receive either HPN-100 + NaPBA placebo or NaPBA + HPN-100 placebo for 2 weeks, and then immediately crossed over (no wash-out period) to receive the other treatment for 2 weeks. The absence of a washout period was not a concern because of the rapid half-life of the drugs. Furthermore, it would be unsafe to have a washout period because interruption of medication could lead to hyperammonemic crisis and irreversible neurologic sequelae or death. Venous ammonia (NH₃_{24-hour} AUC) was the prespecified primary efficacy endpoint. Primary outcome measure assessments were made by admitting subjects to clinical research units for 24 hours of PK blood and urine sampling (including an overnight stay) at the end of each 15-day treatment period, by which time the study drug would be at steady state concentrations.

It was prespecified in the statistical analysis plan that the primary efficacy variable would be natural log-transformed and analyzed using analysis of variance (ANOVA). If the exponentiated upper boundary of the CI was less than or equal to 1.25, then non-inferiority would be concluded. The two treatment groups were also to be compared using the two-sample t-test and the nonparametric Wilcoxon rank-sum test to test significant difference between them. The ITT population was to be used for the primary efficacy analysis and included all subjects who received at least one dose of either study medication. There was one patient who had only one dose of NaPBA and dropped out of study for an AE of hyperammonemia after that. This patient was not included in the final analysis because the patient had not data on Ravicti treatment. It would have been wiser to define the ITT population as the population that received at least one dose of both study medications.

Key prespecified secondary endpoints were:

- Overall correlation between 24-hour urinary PAGN excretion (U-PAGN_{24-hour} Excr) and venous ammonia AUC₀₋₂₄ (i.e. NH₃_{24-hour} AUC) observed at steady state
- Maximum venous ammonia values (i.e. C_{max}) observed at steady state NaPBA versus HPN-100
- Rate (percentage) of ammonia values above upper limit of normal (ULN) observed at steady state NaPBA versus HPN-100

Enrolled patients had to be at least 18 years of age with the following UCDs: CPS, OTC, or ASS, confirmed by enzymatic, biochemical, or genetic testing. They had to be stable on a stable dose of NaPBA for at least 1 week prior to the Day 1 visit with ammonia levels under 100 µmol/L during the 2 weeks preceding screening (subjects could be re-screened after their ammonia was controlled). They could not be on medications that caused decreased renal clearance or increased protein catabolism, had QTc prolongation, known hypersensitivity to PAA or PBA or history of liver transplant. The pivotal trial only enrolled adults. The FDA was responsible for not allowing pediatric patients to enroll in HPN-100-006. We wanted to have some confidence in the safety profile prior to enrolling children in HPN-100 studies, particularly because they were already able to be managed on an approved drug with the same active moiety (NaPBA).

The more severe UCDs are, the less likely the patients are to survive into adulthood. The effect of enrolling adults is that the trial only enrolled patients that were able to survive the worst parts of the disease or had later onset disease which is usually milder. It is possible that the enrollment criteria had the effect of selecting with milder forms of UCDs which decreases the generalizability of the results.

HPN-100 and NaPBA were to be administered orally three times daily (TID) with meals. The identical (PBA mole-equivalent) daily dose of HPN-100 to match the NaPBA daily dose was to be administered to ensure consistent metabolic control for each subject. The reason for this choice was based on the results of study UP1204-003 which indicated similar conversion of PBA to U-PAGN when delivered either as NaPBA or HPN-100 and, therefore, it was determined that HPN-100 had a similar nitrogen-scavenging capacity as NaPBA at mole-equivalent doses (2 moles of NH₃ scavenged to each mole of PBA whether in the form of NaPBA or HPN-100.) The dose of NaPBA was chosen based on the severity of the enzyme deficiency, on the content of the subject's diet, and on the intake of amino acids or other supplements. Therefore, dosing of NaPBA and, therefore, HPN-100, would vary among subjects. If the subject was able to take tablets, they were to be converted to NaPBA tablets (instead of powder) for the purpose of maintaining the blind during the study, for at least one week prior to randomization and throughout the study. No adjustment to the NaPBA or HPN-100 dose or schedule was allowed during the study. Subjects had to follow a stable diet throughout the study as prescribed by the investigator and dietician. As a reminder, there was a double-dummy placebo in each arm of the study to preserve the blind.

At the screening visit, the investigator determined the NaPBA dose for each subject. The 100% HPN-100 dose-equivalent to 100% NaPBA dose was calculated as follows: Because of the heavier molecular weight of HPN-100 than 3 Na PBA molecules (glycerol backbone weighs more than 3 sodiums), 1 gram of HPN-100 = 0.95 grams of NaPBA. And since there is 1.1mL of HPN-100/ g of HPN-100, 1 mL of HPN-100 = 0.86 g of NaPBA.

The maximum total daily dose of HPN-100 allowed in this study was 17.4 mL/day, which corresponds to 20 grams of NaPBA. (It is stated in the Buphenyl label that the safety or efficacy of doses in excess of 20 gm per day has not been established).

The schema was to be as follows:

Screening period: Screening activities could take place within 30 days of Day 1. Baseline assessments included: physical and neurological assessment, measurements of height, weight, vital signs, safety laboratory collection and assessment, urine pregnancy test, ammonia level assessment, 12-lead ECG and HPN-100 dose calculation. An SF-36 questionnaire would also be administered.

Treatment period: Days 1–28 (2 weeks each of NaPBA + HPN-100 placebo and HPN-100 + NaPBA placebo). 24-hour urine collections were to be done prior to receiving the first study dose and were analyzed for NaPBA metabolites. Baseline measurements were to be repeated. At Day 6, 24-hour urine collections were to be initiated for NaPBA and HPN-100 metabolites. At Day 7, subjects were to return to clinic for repeat of baseline measurements. At Day 14, subjects were to return to clinic for end of the 2-week treatment for Period 1 overnight visit for 24-hour blood and urine PK sampling in addition to a repeat of day 6-7 measures. The blood sample PK and ammonia assessments were to occur at 2 and 4 hours after the first dose of study drug (given with breakfast), 4 hours after second dose (8 hours after first dose) (given with lunch), and 2 hours after the third dose (12 hours after first dose) (given with dinner). Additional blood assessments for ammonia and PK were to be done at 16, 20 and 24 hours after the study drug. Day 15 was Day 1 of the second study period. Patients were to be crossed over to the next study drug and the protocol for the second period was to be identical to the protocol for the first study period. No adjustment to the NaPBA or HPN-100 dose or schedule was allowed during the study.

Efficacy Results for HPN-100-006

Disposition and Demographics

46 patients were enrolled in HPN-100-006. 45 patients had at least one dose and were included in the ITT population. 1 patient withdrew on Day 1 before receiving any study treatment because she failed to meet the ammonia control inclusion criterion (152 $\mu\text{mol/L}$). Another patient withdrew after receiving one dose of NaPBA because of hyperammonemia (123 $\mu\text{mol/L}$) and headache due to noncompliance with diet. 44 patients, 22 in each group, completed the 30 day study, and only these patients were actually included in the ITT analysis despite the fact that the protocol prespecified that any patients receiving one dose of any medication would be included. Demographic characteristics were generally well balanced between the treatment arms except the subjects in the NaPBA→HPN-100 arm were older than subjects in the HPN-100→NaPBA arm: mean age of 37.1 years (range: 18 to 75 years) versus mean age of 28.5 years (range: 18 to 55 years), respectively. Most patients were female, white, and had OTC deficiency. Three patients (all female) had ASS deficiency and 2 (1 male, 1 female) had CPS1 deficiency. Nine (20.0%) patients reported a total of 18 hyperammonemic crises within 12 months before study entry and were randomized equally to both arms. The total mean dose during steady-state treatment was similar (13.5 g/d of HPN-100 and 14.01 g/d of NaPBA – which is equivalent to 13.3 g of HPN-100) as was the total dietary protein intake with HPN-100 or NaPBA (45.60 g/d and 41.11 g/d, respectively). Most subjects of the ITT population had childhood (44.4%) or adult onset of UCD (33.3%); neonatal or infantile onset of UCD was each reported in 5 (11.1%) patients. Also, most subjects had OTC deficiency, and there was a preponderance of females in the trial. Females with OTC deficiency generally have milder forms of the disease than their male counterparts. From all this, we can assume that the study enrolled a healthier population of patients than what might be seen in the real world.

Therefore, there is uncertainty about the generalizability of the results of this study to the totality of the UCD population. To balance this, it is likely that the pharmacology of the drug is such that it should work as well in patients that have different enzyme defects, and different degrees of urea cycle function, i.e., severity of disease.

Study Drug Compliance

Compliance with study treatment was excellent regardless of treatment. All patients who completed the study were at least 80% compliant on both NaPBA and HPN-100 treatment; all but one patient were > 90% compliant with study treatment. Compliance with HPN-100 was no better than with NaPBA. Being that this was such a short study (14 days for each treatment), one can not rely on the data to extrapolate long-term compliance.

Efficacy Endpoints

During the study, subjects received a mean (SD) daily NaPBA dose of 14.01 g (6.34) and HPN-100 dose of 13.49 g (5.96). HPN-100 met the prespecified non-inferiority margin relative to NaPBA in controlling blood ammonia assessed as AUC_{0-24} in adult patients with UCDs (upper 95% CI of 1.034, below the predefined non-inferiority upper margin of 1.25). Mean AUC_{0-24} values for blood ammonia were numerically (non-significantly) lower, (~11%) after HPN-100 treatment compared with NaPBA treatment (865.85 ± 660.529 versus 976.63 ± 865.352 $\mu\text{mol}\cdot\text{h}/\text{L}$, respectively) in the ITT population. Therefore, while HPN-100 was shown to be bioequivalent to NaPBA in HPN-100-006, HPN-100 was not shown to be superior to NaPBA.

The mean \pm SD total dietary protein consumed by patients over the 24 hours during which the ammonia was measured was similar during steady state treatment with HPN-100 and NaPBA (47.69 ± 22.788 and 45.89 ± 21.423 g/d, respectively).

The key secondary endpoints were:

- Overall correlation between 24-hour urinary PAGN excretion ($U\text{-PAGN}_{24\text{-hour Excr}}$) and venous ammonia AUC_{0-24} (i.e. $\text{NH}_{324\text{-hour AUC}}$) observed at steady state
- Maximum venous ammonia values (i.e. C_{max}) observed at steady state NaPBA versus HPN-100
- Rate (percentage) of ammonia values above upper limit of normal (ULN) observed at steady state NaPBA versus HPN-100

The correlation between venous blood ammonia and U-PAGN was the only statistically significant secondary endpoint. The other secondary endpoints trended in the right direction: C_{max} values for blood ammonia were 14% lower after HPN-100 compared with NaPBA treatment (60.94 ± 46.213 versus 70.83 ± 66.705 $\mu\text{mol}/\text{L}$, respectively) in the ITT population. The number of ammonia samples above the normalized ULN (35 $\mu\text{mol}/\text{L}$) was similar for HPN-100 and NaPBA treatments in the ITT population (35.6% and 36.2% of samples, respectively). The hatched line across the graph in Figure 9 reflects a mean blood ammonia level of 35 $\mu\text{mol}/\text{L}$, the normalized ULN. One can see that in the first part of the day (post-

breakfast) until somewhere between 4 and 8 hours after breakfast, the mean ammonia level for patients receiving HPN-100 was higher than the mean ammonia level for patients receiving NaPBA after which the pattern switches. Generally speaking, patients are considered hyperammonemic when their ammonia levels are $\geq 100 \mu\text{mol/L}$, because that is when they are at a much greater increased risk of developing neurological sequelae. Some patients, however, have neurological symptoms at lower levels of ammonia than $100 \mu\text{mol/L}$.

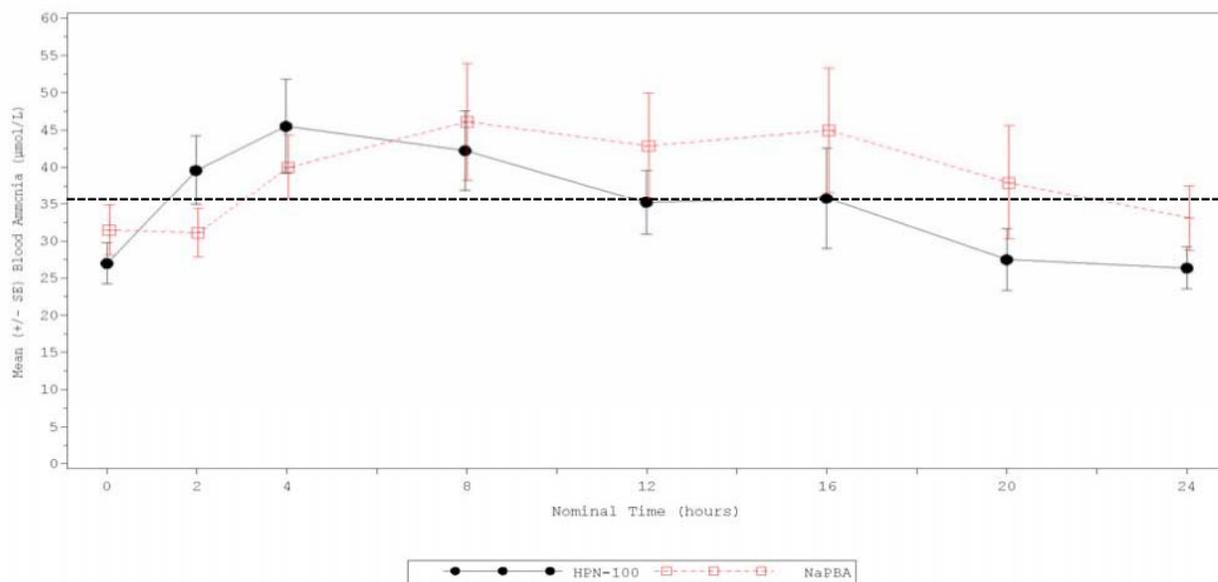


Figure 9: Mean \pm SE 24-Hour Blood Ammonia Values During Treatment with HPN-100 and NaPBA (ITT Population) (doses given at time 0, time 4 hrs and time 10hrs with meals).

Source: Figure 14.2.3.1, p. 68 of the Clinical Study Report HPN-100-006

The majority of patients (25 patients) had time-normalized blood ammonia AUC_{0-24} values \leq ULN during both treatments. Twelve patients had elevated blood ammonia AUC_{0-24} values during both treatments. In 2 patients, blood ammonia AUC_{0-24} values were normal on NaPBA but elevated on HPN-100, while in 5 patients, blood ammonia AUC_{0-24} values were normal on HPN-100 but elevated on NaPBA. Similarly, the majority of patients (26 patients) had normal average daily blood ammonia levels in both treatment arms, while 14 patients had elevated values in both treatment arms. In 1 patient, average daily blood ammonia levels were normal on NaPBA but elevated on HPN-100, while in 3 patients, average daily blood ammonia levels were normal on HPN-100 but elevated on NaPBA. One patient had elevated blood ammonia levels on NaPBA treatment that met the definition of a hyperammonemic crisis ($> 100 \mu\text{mol/L}$).

Approximately 70% of the dose of PBA administered either as NaPBA or HPN-100 was excreted as PAGN in urine over a 24-h period (U-PAGN_{0-24}). There were good correlations between total dose of HPN-100 administered and U-PAGN_{0-24} ($r = 0.795$, $p < 0.001$); and between total dose of NaPBA administered and U-PAGN_{0-24} ($r = 0.800$, $p < 0.001$), (correlation obtained using the Spearman-rank order correlation). There were also very high correlations between dose and plasma PAGN, plasma PAA levels and plasma PBA AUC_{0-24}

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levels [not numerically quite as high as U-PAGN₀₋₂₄ ($r = 0.60-0.76$), using Spearman-rank]. Of important note, there were no significant correlations between ammonia and levels of plasma metabolites. There were no significant differences between treatment groups in any of the metabolites. What this means is that the study failed to reject the null hypothesis that there isn't a difference in these metabolites. It doesn't necessarily mean that there isn't a difference. It could be that the study wasn't designed (powered) sufficiently to demonstrate one. Similarly, it doesn't mean that the metabolite levels were the same.

Subgroup analyses

As shown in Figure 10 (compiling results from studies -006, -005 and UP 1204-003, the mean ratio of blood ammonia during treatment with HPN-100 versus NaPBA, assessed as AUC, was less than one for each subgroup, and all subgroup analyses except for ages 6–11, which included only seven patients, demonstrated non-inferiority (95% CI less than 1.25) of HPN-100 to NaPBA with respect to ammonia control. Likewise, mean C_{max} and average daily values for blood ammonia were consistently albeit not statistically significantly lower with HPN-100 treatment compared with NaPBA treatment across all subpopulations.

The subgroup analysis by age of onset was done for -006 separately and found to trend with the pooled results.

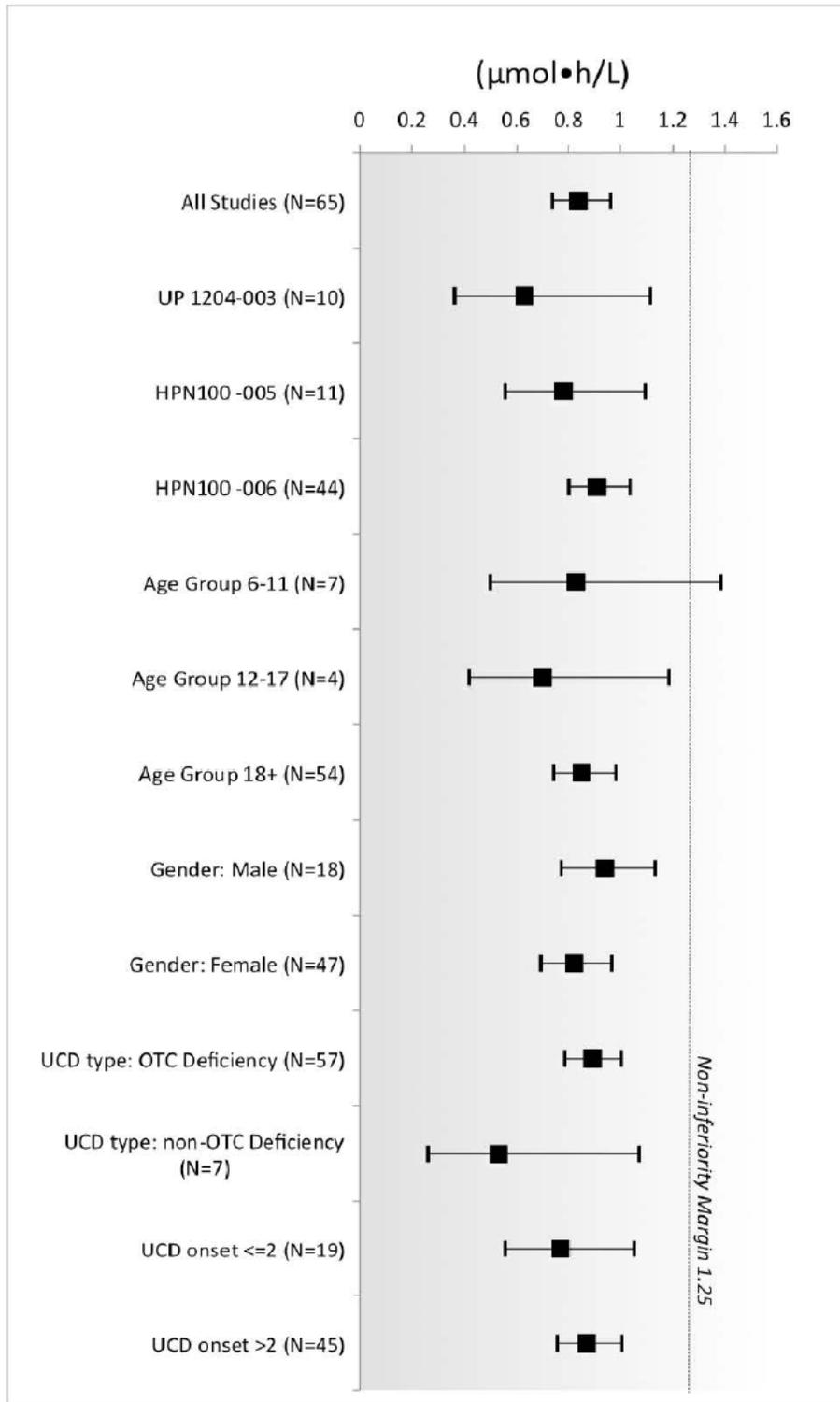


Figure 10: Applicant's Analysis of Blood Ammonia AUC₀₋₂₄ ($\mu\text{mol}\cdot\text{h/L}$) Across Subpopulations (ITT Population) Pooled data from UP 1204-003, HPN-100-005, and HPN-100-006 (short term studies).

HPN-100-007 was the phase 3 OL extension study of HPN-100-006. It was a phase 3, OL safety and efficacy study for the long-term treatment of UCDs. Other participants who did not originally enroll in HPN-100-006 or did not qualify (patients between ages 6 – 17) enrolled. Each patient received HPN-100 orally TID for up to 1 year at either the same dose they had received while participating in HPN-100-006 or, for patients who did not participate in HPN-100-006, at either a PBA-equivalent dose to the patient's NaPBA dose at study entry or a dose calculated by the investigator at screening based on the patient's ammonia-scavenging needs (which was determined based on the patient's protein intake, size, underlying UCD disorder and recent degree of metabolic instability). In this study, dose adjustments were allowed to be made but could not exceed the equivalent of 20 g/day of NaPBA (~17.4 mL total daily dose of HPN-100). Each patient was to follow a stable diet throughout the study as prescribed by the investigator. Patients were evaluated monthly for safety and long-term control of blood ammonia.

Efficacy Results of HPN-100-007

Disposition and Demographics

A total of 60 patients were enrolled in the study, 40 patients from HPN-100-006 and 20 new patients who were naïve to HPN-100, 9 patients under 18 years of age. A total of 53 patients (88%) completed 12 months of treatment, and 7 patients (12%) discontinued. Five patients withdrew consent, 1 patient was withdrawn for AEs (lethargy, gagging, and halted speech considered probably related to the study treatment because ammonia levels were normal), and 1 patient was discontinued for elective liver transplantation. Overall, 68% of patients were female and 32% were male. The majority of patients (51 of 60) were adults. The study population was mostly non-Hispanic white (48 patients [80%]) and included patients who had been diagnosed when they were neonates (13%), infants (15%), children 2–18 years of age (47%), and adults > 18 years of age (25%). Most patients (82%) had OTC deficiency.

Efficacy

Ammonia was well controlled during the study. All mean monthly values were within normal limits. Months 1–12 mean values ranged from 20.7 to 31.3 $\mu\text{mol/L}$ and, except for Month 11 (mean value of 31.3 $\mu\text{mol/L}$), the mean monthly ammonia values were lower than the baseline mean value (27.6 $\mu\text{mol/L}$).

The first phase of **HPN-100-005** was a supportive fixed-sequence, phase 2 OL, non-randomized, active control (NaPBA), switch-over, phase 2 safety and PK/PD study in pediatric patients with UCDs, ages 6-17. Patients were started on NaPBA, three times daily with meals during the first week and were switched to HPN-100 as a single or double stepped procedure. The PBA dose of HPN-100 was equimolar to the PBA dose of NaPBA. Each patient was required to follow a stable diet throughout the 7-day study as prescribed by the investigator and dietician. The primary objectives of the study were to evaluate the safety and PK of HPN-100 compared to NaPBA in pediatric patients with UCDs after 7 days on HPN-100. The primary efficacy endpoint was prespecified as the 24-hour area under the curve for blood ammonia ($\text{NH}_3_{24\text{-hour AUC}}$) on Day 7 for 100% NaPBA and Days 14/21 for 100% HPN-100. The SAP stated that, “an exploratory analysis will be conducted to assess non-inferiority of HPN-100 to NaPBA in ammonia control”.

The second phase of HPN-100-005 was an open-label safety extension phase and was designed to evaluate the long-term safety and ammonia control of HPN-100 in 17 pediatric patients with UCD. Each patient received HPN-100 orally TID for up to 1 year at either the same dose they had received while participating in HPN-100-005 or, for patients who did not participate in HPN-100-005, at a PBA-equivalent dose to the patient's NaPBA dose at study entry. The HPN-100 dose was not to exceed 17.4 mL/d. Each patient was to follow a stable diet throughout the study as prescribed by the investigator. Patients were evaluated at monthly visits for safety and long-term control of blood ammonia. The switch over and extension studies were not powered to assess efficacy. The SAP stated that p-values < 0.05 will be considered to be statistically significant. The SAP also stated that since the study was not powered to detect a statistically significant difference between the treatment groups, and given the small number of subjects, all hypothesis tests will be interpreted as exploratory in nature.

Efficacy Results of HPN-100-005 SO and SE

Disposition and Demographics

A total of 11 patients were enrolled in the study, all of whom completed the study. Most patients were female, white, and had OTC deficiency. One patient had ASS deficiency (male) and one patient had ASL deficiency (female). Four patients reported a total of seven hyperammonemic crises within 12 months before study entry. None of the other patients had hyperammonemic crises before study entry. All patients completed the switch-over phase and enrolled into the long-term safety-extension phase. The total mean daily dose of each study treatment was similar (11.89 mL of HPN-100 and 12.41 g of NaPBA) as was the total mean dietary protein consumed during steady-state HPN-100 or NaPBA treatment (23.98 and 24.35 g/d, respectively). In the switch-over study, there were 7 children ages 6-11 years and 4 adolescents ages 12-17 years.

Seventeen patients (11 children ages 6–11 years and 6 adolescents ages 12–17 years) enrolled in the safety extension and were included in the safety population. The mean age was 10 years (median age was 9 years) and ranged from 6 to 17 years. One patient withdrew consent during Month 11 of the safety extension, and the remaining 16 patients (94%) completed the study.

Efficacy in PK phase (SO)

In an exploratory analysis, HPN-100 was effective in controlling blood ammonia in pediatric patients in the ITT population across multiple analyses. Blood ammonia was non-significantly lower on HPN-100 compared with NaPBA, assessed as AUC_{0-24} (~ 26% lower), C_{max} (~ 14% lower), and the number of ammonia samples that were above the ULN of 35 $\mu\text{mol/L}$ (14 samples from HPN-100 treated patients versus 24 samples from NaPBA patients). Additionally, HPN-100 demonstrated non-inferiority to NaPBA in an exploratory analysis in controlling blood ammonia as AUC_{0-24} (upper bound of the 95% CIs of 1.061; i.e., less than the predefined non-inferiority margin of 1.25).

Efficacy of the Extension Phase

Ammonia was well controlled throughout the study, with similar results in the 6–11 year and 12–17 year age groups. Mean ammonia levels for the safety population were always below the

standardized ULN of 35 $\mu\text{mol/L}$ at each participating site. Results were similar in the two age groups.

When the results of the -007 and -005 extension studies are combined as shown in Figure 11, one can see that the mean ammonia levels were well controlled throughout the extension studies.

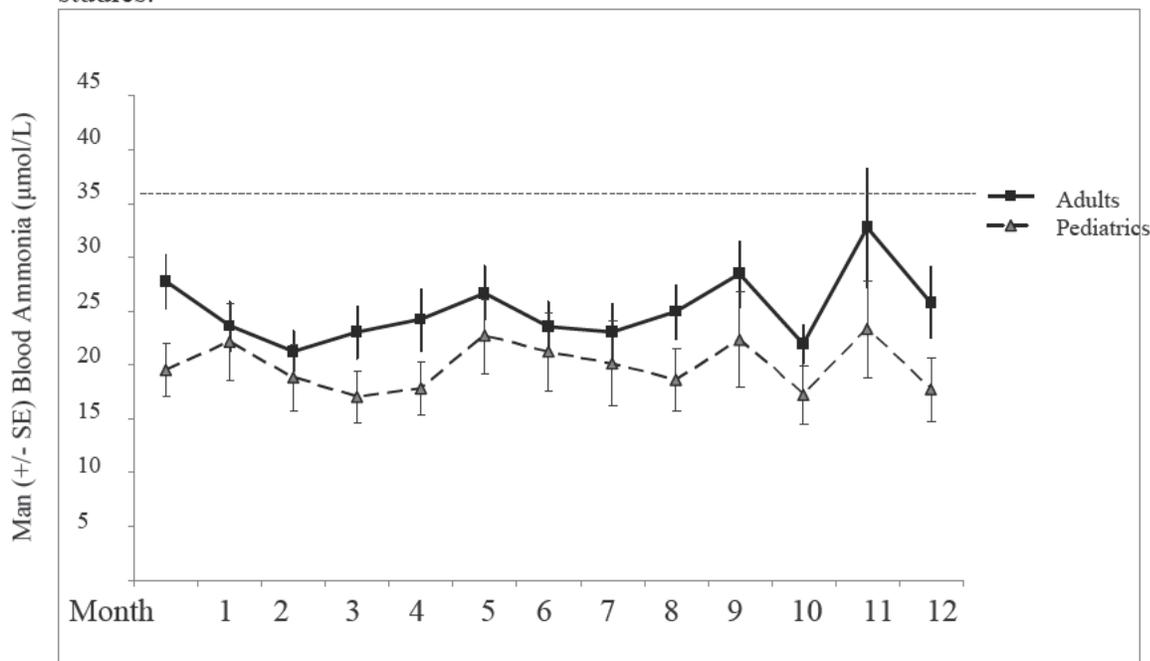


Figure 11: Long-term blood ammonia levels in Patients Treated with HPN-100 (ITT Population) in the open-label studies: HPN-100-005SE and HPN-100-007. 17 pediatric patients from Study -005SE and 9 pediatric patients were from Study -007. 51 Adult patients from -007. 11 of whom were enrolled in the extension phase.

Source: Table 2.3.9 HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; SE = standard error. Note: Mean upper limit of normal among participating sites ~ 35 $\mu\text{mol/L}$, p. 127 of the summary of clinical efficacy in the original submission.

HPN-100-012 was a phase 2 non-randomized, OL, switch-over study in pediatric patients. The main enrollment criteria were that the patients had to be >29 days to six years of age with a UCD, on a stable dose of NaPBA for at least 5 days prior to Day 1, had not undergone liver transplant, had no active infection or catabolic state and had no signs or symptoms of hyperammonemia. Patients were to be switched from Buphenyl to Ravicti with a 10-day assessment period on Ravicti. Study HPN-100-012 was done to meet the Agency's requirement for a study in this age group to avoid the need for a Risk Evaluation and Mitigation Strategy (REMS). The study was not powered to assess efficacy.

Efficacy Results of HPN-100-012

Disposition and Demographics:

Fifteen patients enrolled in and completed the switch-over, including 4 aged 2 months to < 2 years and 11 aged 2 to < 6 years. The study population included 8 male and 7 female patients with a median age of 3 years. Most (80%) were white; 2 patients were black/African-American, and 1 patient was Iranian. UCD subtypes included ASL deficiency (8 patients

[53%]), ASS and OTC deficiencies (3 patients each) and ARG (1 patient) deficiency. Three patients had a G-tube used for medication (NaPBA only) and diet, and none had an NG-tube. No patients used a G-tube for ingestion of HPN-100 through Day 10. Ten of the 15 enrolled patients had at least one hyperammonemic (HA) crisis in the 12 months prior to the study. The number of crises per patient ranged from 0 to 7 (median 1/patient).

Efficacy: In an exploratory analysis, HPN 100 was noninferior to NaPBA in controlling blood ammonia: the upper 95% confidence interval (CI) of 1.055 for 24-hour area under the curve for ammonia ([NH₃24-hour AUC] natural log-transformed scale) was below the noninferiority upper margin of 1.25 predefined for the pivotal trial. Ammonia area under the curve (AUC) was lower on HPN-100 than on NaPBA (median difference of -37.84 $\mu\text{mol/L}\cdot\text{h}$; p-value = 0.075 by paired t-test and 0.033 by Wilcoxon rank-sum test). Mean ammonia levels were non-significantly lower on Day 10 (HPN-100) than on Day 1 (NaPBA) at all time points, as were mean daily average ammonia and peak ammonia levels (daily average: 25 $\mu\text{mol/L}$; peak: 39 $\mu\text{mol/L}$ on HPN-100 vs. 37 $\mu\text{mol/L}$ and 53 $\mu\text{mol/L}$). Mean ammonia levels during HPN-100 treatment were similar in the two age groups (daily average = 27.8 and 24.32 for ages 2 months days to < 2 years and 2 to < 6 years, respectively).

HPN-100-012 Safety Extension (SE) study is an ongoing OL, safety-extension phase of HPN-100-012. This study was designed to evaluate the long-term safety, PK and ammonia control of HPN-100 in UCD pediatric patients ages 29 days to < 6 years of age. HPN-100-012SE was to enroll the patients participating in the switch-over part of HPN-100-012 plus up to an additional 20 patients in the safety extension.

Patients enrolling directly into the safety extension were to be treated with NaPBA at screening for control of their UCD. Each patient received HPN-100 orally TID or QID (for children being fed four times per day) for up to 1 year at either the same dose they had received while participating in HPN-100-012 or, for patients who did not participate in the switch-over phase of HPN-100-012, at a PBA-equivalent dose to the patient's NaPBA dose at study entry. The HPN-100 dose was not to exceed 17.4 mL/d. Each patient was to follow a prescribed diet. Patients were evaluated at Month 1 and 2, then quarterly thereafter for safety, and long-term control of blood ammonia, PK and amino acids.

There was no prespecified efficacy analysis for the SE study.

Efficacy of HPN-100-012 SE

Disposition and Demographics

Twenty-three patients [4 infants (2 months - < 2 years) and 19 children ages 2–5 years) enrolled in the safety extension. The 4 infant patients consisted of one 2-month old, one 3-month old, one 7-month old, and one 11-month old. The most common UCD diagnosis was ASL deficiency (10 patients). AS and OTC deficiencies were the second most common diagnoses (6 patients each) and 1 patient had ARG deficiency.

Efficacy

Results were not included in the submission.

The graph displayed in Figure 12 displays the efficacy results in pediatric patients enrolled in studies HPN-100-012 and HPN-100-005 for the short term data and pediatric patients in study -005SE and -007 for the long term data. The results suggest that Ravicti is effective in controlling venous blood ammonia levels in children age ≥ 2 years. (The 4 patients under 2 years old had adequate ammonia control as well, but the data were too sparse to make conclusions).

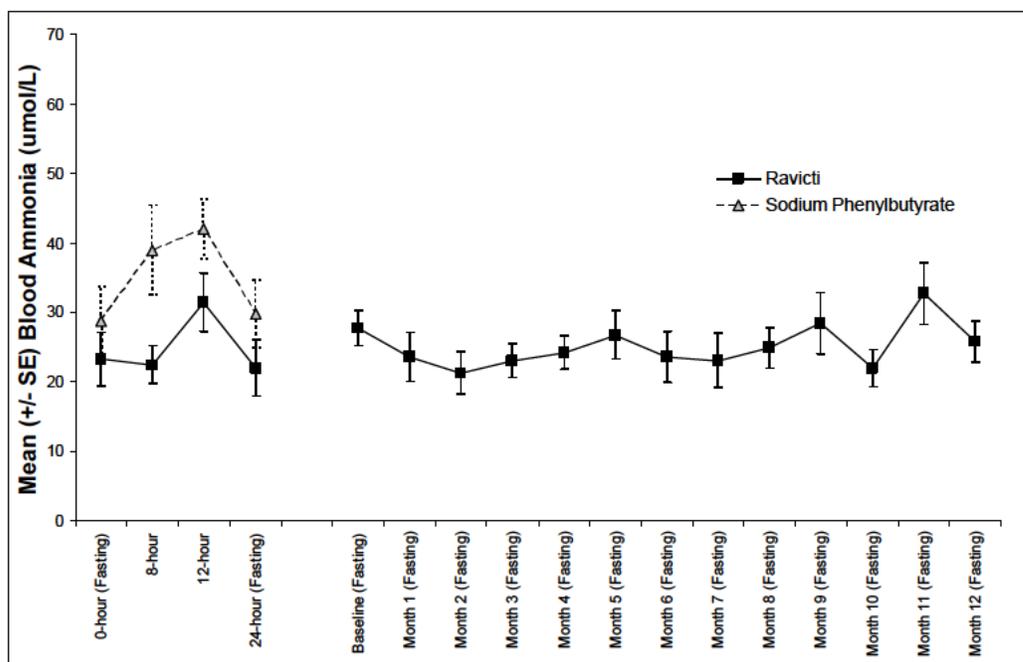


Figure 12: Ammonia Response in Pediatric UCD Patients

Short-Term Studies include 11 patients from study HPN-100-005SO and 15 patients from study HPN100-012. Serial measurements of blood ammonia were performed at steady state after dosing on each treatment. Long-term studies include -005SE (n=17) and pediatric patients enrolled in -007 (n=9).

The following section addresses clinical course in patients who were followed in the long-term studies to address long-term efficacy.

Hyperammonemia Crisis

In HPN-100-007, hyperammonemia crises (ammonia level > 100 $\mu\text{mol/L}$) occurred in 9/60 patient (15% of the patients) over 12 months which was somewhat lower than in the 12 months prior to the study [(10/60 (17%) of patients)]. The average number of crises per patient during the study was 0.20 (12 episodes/ 60 patients vs. 0.27 (16 episodes/ 60 patients) during the 12 months prior. One of the patients (04-7602) had 1 hyperammonemic episode during the Ravicti period and 2 episodes during the year before. Another patient (05-7605) had 2 hyperammonemic episodes during the Ravicti period and 2 hyperammonemic episodes during the preceding year. Another patient (05-7626) had 1 hyperammonemic episode during the Ravicti period and 4 episodes during the previous year. Another patient (05-7701) had 2 hyperammonemic episodes during the Ravicti period and 1 episode during the previous year. Five patients had 6 hyperammonemic episodes during the Ravicti period and none during the year before. Six patients had 7 hyperammonemic episodes during the year before and none during the Ravicti period. The mean and maximum peak ammonia levels during hyperammonemic crises were similar in the 12 months preceding the study (mean 171.16 $\mu\text{mol/L}$, maximum 259 $\mu\text{mol/L}$) and during the study (mean 169.08 $\mu\text{mol/L}$, maximum 239 $\mu\text{mol/L}$). The most frequent precipitating factors were noncompliance with diet (50% of the

total number of crises), noncompliance with UCD medication (31%), infection (31%), and intercurrent illness (25%). In HPN-100-005 extension, three of 17 patients (18%) had a total of three hyperammonemic crisis during the 12-month safety extension, which was fewer than the number of patients (5 [29%]) who had reported a total of 8 hyperammonemic crises in the 12 months prior to the study. No precipitating factor was reported for any of these crises.

In the extension study, HPN-100-012 SE, there were 3 patients who developed hyperammonemia. That is 13.6% of patients at the time of the 120-day update when the average length of exposure was 3 ½ months. Two of the three patients had had hyperammonemic episodes when on Buphenyl (one had 7 episodes the year prior and two episodes within 3 months on HPN-100; one had 2 episodes the year prior and 1 episode after enrolling in the extension study. The third patient was 2 months old when she started on the first phase of study -012 and comparison to a previous period is not possible.

These data provide evidence that HPN-100 is at least as effective as Buphenyl in controlling ammonia for up to at least 12 months of treatment, at least for patients age 6 and above.

Clinical Endpoints

There was no formal hypothesis testing for the neuropsychological outcomes but I thought the results of this testing were interesting enough to add to my review. In the long-term extension study of HPN-100-005 and HPN-100-007 both at the time of enrollment and after 12 months of treatment with HPN-100 or at time of study exit. WASI® (for intellectual ability in adult and pediatric patients) and other age appropriate tests were administered to adult and pediatric patients: the grooved pegboard test (for motor and visual skills through manual dexterity), the California Verbal Learning Test (CVLT) to test verbal memory abilities, and the digit span test for adults to test short term memory and attention, and BRIEF® to evaluate pediatric executive function and CBCL® to evaluate behavior in pediatric patients. There was no prespecified hypothesis testing. Hence, these were exploratory tests.

Most of the performance on these tests remained stable during the year long treatment period. Only the BRIEF® testing had a numerical improvement with a very low p value, particularly for metacognition index and global executive function. However, this was not a prespecified endpoint and the results are subject to type 1 error. The applicant (b) (4)

8. Safety

The safety database for Ravicti includes data from 9 controlled and 3 uncontrolled clinical studies in 268 subjects who received at least one dose of HPN-100. These subjects included 112 UCD patients (65 adults, 26 children between the ages of 6 and 17 years and 22 patients < 6 years old) with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH across five studies (UP 1204-003, HPN-100-005, HPN-100-006, HPN-100-007, and HPN-100-012SE). A

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description of the studies is shown in Table 4. Safety data is also available for 39 patients without UCIDs who had hepatic impairment from two studies (UP 1204-002, HPN-100-008 Part A) and 130 healthy adults, including 32 enrolled in two Phase 1 single- and multiple-dose pharmacokinetic(PK) / pharmacodynamic(PD) studies (UP 1204-001, UP 1204-002) and 98 enrolled in a thorough QT/QTc study (HPN-100-010).

77 patients with UCIDs have completed 12 months of HPN-100 as of the time of original submission of the NDA (51 adults from HPN-100-006, 26 pediatric patients age 6-17 years). Most of these patients (43 adults and 24 pediatrics age 6-17 years) are now enrolled in the continuing access protocol, HPN-100-011.

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Table 4: Summary of HPN-100 Clinical Studies Included in the NDA

Study Number	Phase	Study Design	Study Objective	Subject Status/ Patient Diagnosis	Safety Population: Number Exposed to HPN-100
Subjects					
UP 1204-001	1	Randomized (R), Open-Label (OL), Cross Over (X)	PK	Healthy	96
UP 1204-002	1	Uncontrolled	PK	Hepatic or healthy	32
HPN-100-008, Part A	1	R, OL, run-in	Hepatic Impairment	Hepatic or healthy	15
HPN-100-010	1	R, Double Blind (DB), X	Thorough QTc	Healthy	98
Patients					
UP 1204-003	2	Non-R, OL, fixed-sequence, switch-over	Safety and efficacy	Adult UCD	14
HPN-100-005	2	Non-R, OL, fixed-sequence, switch-over followed by a long-term OL phase	Safety and efficacy	Pediatric UCD	11
HPN-100-006	3	R, DB, X	Safety and efficacy	Adult UCD	45
HPN-100-005 Safety extension	2	Non-R, OL, fixed-sequence, switch-over followed by a long-term OL phase	Safety and efficacy	Pediatric UCD	17
HPN-100-007	3	Uncontrolled	Safety	Adult and Pediatric UCD	60
HPN-100-011	2	Uncontrolled	Safety	Patients from HPN-100-007 + HPN-100-005 Safety extension	67
HPN-100-012 switch-over	2	Non-R, OL, switch-over	PK Safety	Pediatric UCD	15
HPN-100-012 Safety extension	2	OL, safety extension	Safety and efficacy	Pediatric UCD	22

A brief description of the above safety studies are listed below:

UP 1204-001 was a phase 1, randomized, cross-over, open-label PK and safety study of HPN-100 and oral NaPBA in 32 healthy subjects. The dose of HPN-100 was 3g/m² for one day with a NaPBA comparator.

UP1204-002 was an active control, switch over phase 1, open-label safety and PK/PD study of HPN-100 in subjects with hepatic impairment and cirrhosis (n=24) and in age- and gender-

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matched control subjects with normal hepatic function (n=8). The study was of 2 weeks in duration. Upon enrollment, subjects received NaPBA for 7 days and were then admitted to a study unit for overnight observation and 24-hour PK, ammonia measurements, amino acids, and urine collections. They were then switched over to HPN-100 at 200 mg/kg/day for 7 days and returned to the study unit for the same observations.

UP1204-003 was a phase 2, open-label, fixed sequence, switch-over study of the safety, tolerability, PK and PD of HPN-100 compared to NaPBA in adult subjects with UCDs conducted at 4 US centers and enrolling 14 adult UCD patients, 10 of whom completed the study. All subjects who received at least one dose of HPN-100 completed the study. Subjects were then converted to the PBA equimolar dose of HPN-100. Subjects stayed on the 100% HPN-100 dose for 7 days and were then re-admitted to the study unit for repeated 24-hour PK, ammonia, amino acids, and urine collections. No prespecified testing of hypotheses was performed as part of the planned efficacy and safety analyses.

HPN-100-005, HPN-100-006, HPN-100-007 and HPN-100-012 and the **HPN-100-012 safety extension** study were discussed in detail in the efficacy section. HPN-100-012 SE is ongoing. There are 22 patients enrolled including 15 from HPN-100-012.

HPN-100-008 was a phase 2 study in subjects with hepatic encephalopathy (HE) that consisted of an OL safety lead-in (Part A) followed by a randomized, double-blind, placebo controlled treatment (Part B). Only Part A of the study is included in the ISS. Part B is ongoing and blinded at this time. Part A is an open-label, dose-escalation lead-in to assess HPN-100 safety and PK. Approximately 10 subjects with HE and cirrhosis classified as Child Pugh B or C will undergo a one-step dose escalation over 4 weeks. Subjects will initially receive 6 mL HPN-100 BID for 1 week. On Day 8 and following satisfactory safety assessment of the subject, the dose will be escalated to 9 mL BID for an additional 3 weeks.

HPN-100-011 provides UCD patients who completed either HPN-100-007 or -005 with continued access to HPN-100. There is ongoing data collection from this study. 67 patients were enrolled at the time of the 120-day safety update.

Safety Results

Deaths

No UCD patients died during this development program. In the study of hepatically impaired patients without UCDs, 5 hepatically impaired patients died, one of hepatic failure, two of gastrointestinal hemorrhage, two of acute renal failure. Two patients died in HPN-100-008 Part A, an uncontrolled study. Part B, in which there were 3 deaths, was placebo-controlled. At the time of the study reports, Part B was not yet unblinded. With the information that we have access to, is not possible to assess if HPN-100 worsens complication of hepatic failure. It is also not clear from the results of study HPN-100-008 Part A that HPN-100 is effective at reducing ammonia levels. Therefore, it is prudent to state in the label that it is unknown if Ravicti is safe or effective in patients with advanced liver failure.

The following are capsule narratives for each hepatically impaired patient death.

HPN-100-008 Part A—Patient 06-001 (renal failure): A 57-year-old white female, Child-Pugh classification B with a medical history significant for HCV infection, cirrhosis, hepatic encephalopathy, recurrent ascites, hypertension, diabetes mellitus type II, schizoaffective disorder with major depression, gastroesophageal reflux disease, and chronic obstructive pulmonary disease, experienced Grade 3 liver failure 2 weeks after progressing to HPN-100 treatment at 9 mL BID from 6 mL BID, discontinued treatment with HPN-100 on Day 24, and died from renal failure on Day 41. At the Day 14 visit, she was dehydrated, with swollen legs and abdominal pain, distension, and tenderness. She complained of extreme fatigue and some confusion, her speech was slow and slurred, and she had slight asterixis. She went to the emergency room (ER), where she was given 1 L of IV fluid and released. Over the next 3–4 days, she experienced abdominal fluid retention and returned to the ER for abdominal pain, rigidity, and distension. Her model for end-stage liver disease (MELD) score was 20 (increased from 12 at baseline). She did not receive any treatment. She had the same complaints at her Day 21 visit and was hospitalized in the intensive care unit the following day with abdominal distension secondary to fluid overload, pain exacerbated by movement, nausea, vomiting, yellow diarrhea, anorexia, confusion, and loss of balance with falls. She had hyponatremia secondary to increased water intake, resulting in volume overload with large ascites, which was treated with paracentesis, fluid restriction, and IV furosemide. She was discharged from the hospital 3 days after discontinuing HPN-100 treatment with no signs of encephalopathy.

She was readmitted to the hospital 2 days later due to altered mental status secondary to hyponatremia, difficulty speaking, ascites, peripheral edema, and increased jaundice. A computed tomography scan revealed a hypervascular mass (3 cm) consistent with hepatocellular carcinoma, splenomegaly, gallstones, varices, and ascites, and she was found to have developed acute-on-chronic renal injury. She was discharged to hospice care after 7 days and then readmitted to the hospital 3 days later (Day 40, 16 days after the last dose of HPN-100) with renal failure (creatinine 3.67 mg/dL) and abdominal pain and distension. The patient had “Do Not Resuscitate” orders in place, and only comfort measures were administered. She died of acute renal failure the following day. The investigator assessed the event of liver failure as possibly related to study treatment. In his assessment of potential causes of this patient’s deterioration and increase in serum transaminase activity, the investigator judged study treatment toxicity as least likely but impossible to exclude. Renal failure was considered not related to study treatment. Iohexol (IV contrast dye) was considered a co-suspect medication in the event of renal failure.

HPN-100-008 Part A—Patient 61-407 (esophageal varices hemorrhage): A 50-year-old white male, Child-Pugh classification C with a medical history significant for liver cirrhosis, esophageal varices, and hepatic encephalopathy, died of esophageal varices hemorrhage 14 days after progressing to HPN-100 treatment at 9 mL BID. The last dose of HPN-100 was on Day 12. On Day 13, he experienced multiple episodes of vomiting with blood. He was transported to the hospital with bleeding esophageal varices and hypovolemic shock. He was treated with blood transfusions and blood replacement products and with Ethamsylate and aminocaproic acid. His condition worsened, and he died the following day. Autopsy showed small nodule liver cirrhosis, splenomegaly, esophageal varices with erosion, blood in the stomach and intestines, and anemia of the internal organs. The event was considered not related to HPN-100 treatment.

HPN-100-008 Part B—Patient 37-326 (hepatic insufficiency): A 44-year-old white female,

Child-Pugh classification C with a medical history significant for alcohol abuse, liver cirrhosis, hepatitis B and C, ascites, and portal hypertension experienced Grade 4 spontaneous bacterial peritonitis and died of hepatic insufficiency 16 days and 54 days, respectively, after initiating HPN-100/Placebo treatment (6 mL BID).

The patient received her first dose of HPN-100/Placebo on (b) (6). Starting in the evening on (b) (6), she experienced abdominal pain (greater in the lower abdomen). On (b) (6), she had a fever of 39 °C and experienced dyspnea while supine, weakness, and lethargy. A test of ascetic fluid confirmed peritonitis. She was treated with cefotaxime and metronidazole. The patient went into a coma on (b) (6). Treatment with HPN-100 was discontinued. She was transferred to intensive care and treated with L-ornithine-L-aspartate, prednisolone, and IV fluids. Her lactulose dose was increased. On (b) (6), she opened her eyes and reacted to simple commands, and she was transferred out of intensive care. Treatment with HPN-100 was resumed on (b) (6). On (b) (6), she was found to have an increased INR and increased creatinine, urea, and bilirubin. She was diagnosed with toxic nephropathy with partial renal insufficiency and liver failure. Her condition became stable on (b) (6). On (b) (6), the peritonitis was considered resolved with the sequela of increased bilirubin (Grade 3). She had a new HE event (Grade 3) from (b) (6). HPN-100-008 study treatment was discontinued permanently on (b) (6). This HE event was considered resolved on (b) (6). On that date, ALT was 16, AST was 31, and total bilirubin was 6.1 On (b) (6), ALT was 30 U/L, AST was 46 U/L, and total bilirubin was 164.2 µmol/L. She was discharged from the hospital on (b) (6), assessed as clinically stable. According to her family, she was grossly noncompliant with her prescribed diet after discharge. The patient died on (b) (6). The postmortem examination listed the main diagnosis as hepatic cirrhosis of mixed etiology, complicated by hepatic insufficiency and decompensation. The immediate cause of death was shown as cerebral edema. The investigator assessed these events as not related to study treatment.

HPN-100-008 Part B—Patient 38-343 (gastrointestinal hemorrhage): A 54-year-old white male, Child-Pugh Classification B with a medical history significant for hepatitis C, hepatic cirrhosis, chronic cholecystitis, chronic pancreatitis, polycystic left kidney, and chronic pyelonephritis died due to GI bleeding 82 days after initiating HPN-100 (6 mL BID).

The patient began receiving study treatment on (b) (6). On (b) (6), he began vomiting blood and was taken by ambulance to the hospital. An esophagogastroduodenoscopy procedure was performed, and he was found to have esophageal varicose vein dilatation. Diagnoses during hospitalization were decompensated liver cirrhosis, portal hypertension syndrome, bleeding esophageal varices with severe hemorrhage, hepatic insufficiency, and coronary heart disease. He died on (b) (6). The death certificate listed the causes of death as anemia, bleeding esophageal varices, and hepatic cirrhosis. The investigator assessed this event as not related to study treatment.

HPN-100-008 Part B---Patient 74169 (acute kidney failure): A 67-year-old white female with baseline MELD of 21, experienced two events of Grade 3 hepatic encephalopathy, a Grade 3 pelvic fracture, and a Grade 3 humerus fracture, and died of acute kidney injury two weeks after discontinuing blinded study drug. The AE resulting in death was renal failure (acute kidney failure) and the death was considered unrelated to study drug.

During the short-term studies, both NaPBA and HPN-100 were generally safe and well tolerated. In study HPN-100-006 and HPN-100-005SO, no hyperammonemic crises were

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reported in patients on HPN-100 and no patients discontinued HPN-100 treatment because of an AE.

There was one patient who withdrew from the pivotal study. The patient was on NaPBA treatment at the time of withdrawal and withdrew because of an SAE; high blood ammonia levels (123 µmol/L) and headache on Day 1 of the study. The high ammonia level was attributed to noncompliance with diet.

There was 1 SAE in HPN-100-006 that did not result in discontinuation. The patient (20-639), a 19-year old Hispanic male with OTC deficiency had gastroenteritis (attributed to food poisoning) on day 10 when on NaPBA.

During the short-term studies, no hyperammonemic crises were reported with HPN-100 and no patients discontinued HPN-100 treatment because of an AE.

Most AEs were rated as mild in intensity. Symptoms suggestive of lower GI disorders (e.g. diarrhea and flatulence) were reported more frequently on HPN-100 treatment. Symptoms suggestive of upper GI disorders (e.g., abdominal discomfort and dyspepsia occurred equally on both treatments in the pivotal trial. Nausea occurred more often in patients on NaPBA (3 compared to 1). These events were generally mild, not serious, and did not result in patients withdrawing from the study. In the pivotal trial, headache (~14%) was a common AE for both treatments. The relative risk for headache in HPN-100-006, the only trial which was acceptable for comparison to NaPBA, was 1. Dizziness was reported by more patients treated with NaPBA than HPN- 100 (4(8)% versus 0) in study HPN-100-006.

No notable patterns of changes in vital signs, ECGs (including changes in QTc intervals based on triplicate recordings), or safety laboratory values (hematology, chemistry, or urinalysis) were observed during HPN-100 or NaPBA treatment.

In Table 5, most treatment emergent AEs (TEAEs) are listed that occurred during either treatment in the HPN-100-006. Certain AEs such as arthropod bite and pain from braces being tightened were left out of the table. A TEAE was defined as an AE that begins (or a preexisting AE that worsens) after receiving the study medication through 7 days after the last dose of study medication.

For dizziness alone, because there was such a wide disparity between treatment groups, in order to calculate a relative risk, I added a 1 to both treatment groups (see the key to the table).

Diarrhea, flatulence, vomiting and headache were the most common AEs that could be reasonably attributed to Ravicti. The only episode of hyperammonemic crisis in HPN-100-006 was in one patient on NaPBA who received only one dose of NaPBA. This is reassuring but it must be kept in mind that the controlled period was only 2 weeks for each treatment, making it difficult to make firm conclusions. In fact, there were cases of hyperammonemic crisis in the long-term studies that were discussed in the efficacy section of this review and in Dr. Snow's clinical review. The only AEs that stood out as being much more common in one group than the others were dizziness (~5 times more common in the NaPBA treatment arm, although

calculated by adding a case of dizziness to HPN-100), and flatulence (~6 times more common in the HPN-100 treatment arm). All AEs except for gastroenteritis were in the mild to moderate category.

Table 5: TEAE from controlled adult study HPN-100-006

System Organ Class	HPN-100	NaPBA			
Preferred Term (Medra 12.1)	n=44 44	incidence	n=45 45	incidence	RR
GI disorders					
abdominal pain or discomfort	5	0.11	5	0.11	1.02
constipation	0	0.00	1	0.02	0.00
diarrhea	7	0.16	5	0.11	1.43
dyspepsia/ GERD/ excessive burping	3	0.07	3	0.07	1.02
nausea	1	0.02	3	0.07	0.34
vomiting	3	0.07	2	0.04	1.53
flatulence	6	0.14	1	0.02	6.14
decreased appetite	3	0.07	2	0.04	1.53
increased appetite	0	0.00	2	0.04	0.00
General disorders		0.00		0.00	
fatigue	3	0.07	2	0.04	1.53
pyrexia	1	0.02	0	0.00	
Infections and infestations		0.00		0.00	
gastroenteritis	1	0.02	0	0.00	
nasopharyngitis	1	0.02	0	0.00	
upper respiratory infection	1	0.02	0	0.00	
Protein and amino acid metabolism disorders		0.00		0.00	
hyperammonemia (> 100)	0	0.00	1	0.02	0.00
Laboratory Investigations		0.00		0.00	
Ammonia increased	2	0.05	1	0.02	2.05
Hemoglobin decreased (0.9 gm)	0	0.00	1	0.02	0.00
Musculoskeletal disorders		0.00		0.00	
neck pain	0	0.00	1	0.02	0.00
extremity pain	1	0.02	1	0.02	1.02
Nervous system disorders		0.00		0.00	
dizziness	1	0.02	5	0.11	0.20
headache	6	0.14	6	0.13	1.02
syncope	1	0.02	0	0.00	
Respiratory disorders		0.00		0.00	
cough	1	0.02	0	0.00	
oropharyngeal pain	0	0.00	1	0.02	0.00
Skin disorders		0.00		0.00	
rash/ dermatitis/ eczema	0	0.00	1	0.02	0.00
abnormal skin odor	0	0.00	1	0.02	0.00

Source: From the AE data set for HPN-100-006, using JMP and EXCEL

Only for common AE dizziness, which was very high incidence in NaPBA and none in HPN-100 did I add a one to both treatment groups for the purposes of calculating a Relative Risk (RR)

As for the uncontrolled study AEs, I combined the AE datasets from -005 SO, -005 SE, and -007 which included 77 patients in all, 51 adults and 26 children. I did not consider the AEs from -012 in this analysis because they were not studied for 12 months. As you can see in Table 6, there was a high incidence of gastrointestinal symptoms but there were few complaints of flatulence, suggesting that tolerance to this symptom is achieved after the first 2 weeks on treatment. Upper respiratory infections were common. Headache and dizziness were

the most common neurological AEs. 4% of patients had “convulsions” or seizures. This is concerning, but it is unclear if the seizures are related to the patients underlying condition. UCDs are associated with a higher risk of seizure disorder. Cough, rash, elevated LFTs, hyperammonemia, and menstrual difficulties were also common. Most AEs were mild to moderate in severity. There were 7 cases of hyperammonemia that were severe but patients recovered. The loss of vision was severe but the patient recovered. The case of ventricular fibrillation was not marked for severity, but the patient did recover. The other severe AEs were mostly gastrointestinal symptoms from which the patients recovered.

In study -007, there was one case of a “mild” spontaneous abortion that occurred 2 weeks after study end date in a 24 y/o white female that was not considered to be related to the drug. In study-005SE, patient HPN- 05-5051 had a case of “mild” thrombocytopenia, 64 K that occurred during an upper respiratory infection and recovered to 187K by the next laboratory visit, 4 months later.

In study -007 there was one case of sudden loss of vision which was considered to be severe. The patient recovered. The relationship between these events and Ravicti is not clear.

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Table 6: TEAEs from the open label studies: -005SO (7 days), -005SE (12 months), and -007 (12 months), 51 adults and 26 children ages 6-17, (source: data sets from these studies), Meddra 12.1 used for AE terms

		n-77	%
		#	
		patients	
		with	
		events	
Cardiac	Ventricular Fibrillation	1	(1)
	Sinus arrhythmia	1	(1)
GI disorders			
	Abdominal discomfort, pain, distension	17	(22)
	constipation	4	(5)
	diarrhea/urgency	14	(18)
	dyspepsia/gastritis	6	(8)
	flatulence	3	(4)
	nausea	15	(19)
	oropharyngeal pain	12	(16)
	vomiting/retching	25	(32)
General disorders			
	hyperammonemia	12	(16)
	fatigue/ lethargy	11	(14)
	pyrexia	7	(9)
	Edema, peripheral	2	(3)
Infections			
	influenza	6	(8)
	naopharyngitis/sinusitis	30	(39)
	pneumonia	1	(1)
	bronchitis/URI	31	(40)
	gastroenteritis	10	(13)
Investigations			
	LFT elevations	6	(8)
	ammonia increased	1	(1)
	Anion Gap increase	2	(3)
Metabolism and nutritional disorders			
	decreased appetite	12	(16)
	increased appetite	4	(5)
Musculoskeletal disorders			
	Back Pain	6	(8)
	Joint/ Extremity Pain	7	(9)
Nervous System Disorders			
	Sudden Vision Loss	1	(1)
	Convulsions/ Seizure	3	(4)
	Peripheral Neuropathy	5	(6)
	Tremor	3	(4)
	Headache	17	(22)
	Dizziness	9	(12)
Psychiatric Disorders			
	Insomnia	3	(4)
	Irritability/Aggression	2	(3)
	Anxiety/ Depression	3	(4)
Respiratory Disorders			
	Asthma	2	(3)
	Cough	11	(14)
Skin Disorders			
	abnormal skin odor	7	(9)
	Rash/ Dermatitis	13	(17)
Other			
	Menstrual Difficulties	7	(9)
	Anemia	1	(1)
	Thrombocytopenia	1	(1)
	Leukopenia	1	(1)
	Lymphadenopathy	1	(1)

The SAEs in the long term studies were examined in another analysis. See Table 7. As expected, the most common SAEs were hyperammonemia. Again, patients with more than one episode would only be counted once, so this analysis of hyperammonemia is not the same as the one presented in the efficacy section which counted episodes of hyperammonemic crisis as well as patients affected. The hyperammonemia episodes included in this section do not necessarily rise to the level of crisis which is > 100 µmol/L along with neurological symptoms. The patient who had the pulmonary infiltration/infection, had not recovered at the time of the NDA submission. All other SAEs had recovered.

Table 7: SAEs in uncontrolled studies HPN-100-007 and HPN-100-005 SE, with 77 patients, 51 adults and 26 children ages 6-17(source: data sets from these studies)

	n=77	
	# Patients with SAEs	%
Abdominal Pain	1	(1.3)
Gastroenteritis	2	(2.6)
Vfib	1	(1.3)
Dizziness	1	(1.3)
Hyperammonemia with or without complications	12	(15.6)
Hyperammonemia with Infection	1	(1.3)
Hyperammonemia with Psychotic Features	2	(2.6)

In study HPN-100-012 SE, There were 3 patients of 22 who were enrolled in HPN-100-012 SE, who had SAEs related to hyperammonemia, 2 had infection and one had no complications of infection or psychotic features. These patients were not included in the above table.

Laboratory Changes during the Controlled Trials in UCD

Hemoglobin: In the controlled period of HPN-100-006, there was a mean hemoglobin decrease of 0.54 g/dL in UCD patients on HPN-100, but only a mean decrease of 0.08 in patients on NaPBA. One patient had a 2.6 g/dL drop in hemoglobin on HPN-100, whereas, the lowest hemoglobin drop on NaPBA was 1.7 g/dL. The maximum increase was 1.0 g/dL on HPN-100 and 1.9 g/dL on NaPBA. The median drop in hemoglobin in patients on HPN-100 was 0.5 g/dL. The median drop in hemoglobin in patients on NaPBA was 0.1 g/dL.

There was one hemoglobin drop AE in study HPN-100-006: A 43-year-old American Indian/Alaskan Native female randomized to NaPBA→HPN-100, experienced a mild (CTCAE Grade 1) decrease in hemoglobin from 11.8 g/dL on Day 1 to 10.9 g/dL on Day 8 while on NaPBA treatment (normal range: 12.0–16.0 g/dL). The investigator considered the decreased hemoglobin to be not related to study treatment but related to the patient’s UCD. The patient’s hemoglobin remained decreased throughout the duration of the study (10.7–10.9 g/dL through Day 28).

In study HPN-100-005 in the 6-17 year olds, there was a 0.24 g/dL mean decrease in hemoglobin while on HPN-100 and a mean decrease of 0.03 g/dL while on NaPBA. The

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maximum decrease was 1.2 g/dL on HPN-100 and 1.0 g/dL on NaPBA. The maximum increase was 0.7 g/dL on HPN-100 and 1.0 g/dL on NaPBA.

During the HPN-100-005 safety extension study, a 17-year-old African-American female had a decreased hemoglobin value (100 g/L) at Month 11 that was considered clinically significant. All other hemoglobin values during the study were low but not clinically significant. At Month 1 (first value on the extension study), hemoglobin was 10.4 g/dL (normal range 12.0–15.0 g/dL), and it was 110 g/L at the last value.

In the pooled short-term studies, shift tables were done for the Ravicti arm only. For hemoglobin, 15.4% of patients on HPN-100 who started with normal levels shifted to low values while 2.6% shifted to high levels. 33.3% of patients who started with low hemoglobin levels shifted to normal. The others who started low stayed low. These observations taken together with the mean drops in hemoglobin referenced above and the outliers, suggested the presence of an anemia signal. Upon further investigation into the results of the long-term safety extension studies, there was no decrease in hemoglobin compared to the beginning of the extension studies. Therefore, there is no concerning anemia signal, after all.

In HPN-100-007, the mostly adult safety extension study (9 children, 51 adults), mean baseline hemoglobin was 13.5 g/dL (min 10.4, max 16.4) and at 12 months, the mean hemoglobin was 13.5 g/dL (min 11.1 g/dL, max 14.5 g/dL).

In HPN-100-005 SE, patients started at a mean baseline of 12.5 g/dL (min 10.7 g/dL, max 15.1 g/dL) hemoglobin. It is reassuring that at the end of 12 months, the mean hemoglobin was 12.9 g/dL (min 11.4 g/dL, max 14.3 g/dL).

No patients required transfusion during the studies in UCD pts. And there were no bleeding AEs during any of the studies in UCD patients.

Taken together, it is most likely that the drops in hemoglobin seen in the short term studies were a combination of chance and regression to the mean.

There were no notable mean changes in **white blood cell counts or platelets** or in median values or extreme values.

There were no notable mean changes in **electrolytes and liver function tests** or in median values or extreme values. There were no Hy's law cases and only one case of isolated increase in bilirubin (not accompanied by LFT increases).

There were no notable mean changes in **coagulation profiles** or in median values or extreme values.

There were no notable mean changes in **ECGs**. As mentioned on pages 35-36, there were two patients with QT prolongations and one patient who had ventricular fibrillation while having liver transplantation. The level of metabolites was probably very low in the patient who had the transplantation because it was done on the day following Ravicti discontinuation. The

patients with the QT prolongation did not have arrhythmias and it is not clear that these changes were related to drug. While it would be ideal to have the QT study repeated because of the lack of assay sensitivity, the QT results of the Ravicti did not reveal an upswing and the data were not highly variable. For these reasons, it is considered unlikely that Ravicti will increase the QT interval by ≥ 10 ms, even knowing that there was no assay sensitivity. For this reason, it is not necessary to repeat the QT study for approval.

Safety in the 1-year extension studies in patients age 6 years to adult

As stated earlier, five patients withdrew consent prior to the end of the 12 month period of HPN-100-007 and -005. **Patient 02-7701** withdrew after several AEs, including rash, facial edema, decreased appetite, dysgeusia and UTI. The rash and facial edema were not considered severe and did not result in hospitalization. It may have been an allergic reaction, but there were no other clearly allergic reactions in the development program. The patient also developed one SAE (pneumonia) prior to withdrawing. **Patient 05-7640** discontinued after multiple AEs (increased appetite and sweating) and then developed an SAE (psychosis) followed by an SAE of hyperammonemia related to an intercurrent illness. **Patient 07-7714** had headaches, paresthesias, somnolence, dizziness, metrorrhagia, and hot flashes among other AEs. She had a total of 30 AEs after starting treatment, all mild to moderate in intensity. The patient had a complete recovery. **Patient 18-7624** withdrew after AEs of retching, anorexia, speech disorder, back pain, tremors, lethargy, and nausea and vomiting. The patient's ammonia level was 24 $\mu\text{mol/L}$ at the early termination visit and no PAA levels were available. **Patient 12-7612** had ventricular fibrillation which occurred during a liver transplantation that occurred the day after stopping HPN-100. This was considered to be an SAE.

The safety results of the HPN-100-012 switch-over study and the HPN-100-012 (Safety Extension) study were not included in the summary of safety above because the data were submitted in a 120-day safety update and are, therefore, considered separately. The safety results from study HPN-100-011 were also included in the safety update and are considered separately. HPN-100-008 is considered separately because it pertains only to hepatically impaired patients without UCDS.

HPN-100-012

In this study of 15 children ages 2 months to 5 years old, 6 patients (40%) experienced AEs on HPN-100, all mild in severity. 2 patients had vomiting who had been taking NaPBA via gastrostomy tube but took HPN-100 orally. Other AEs on HPN-100 were lymphadenopathy, flatulence, cardiac murmur and rash. These occurred only in single patients. There were no concerning changes in laboratory tests during or after 10 days of HPN-100. No patients had AEs leading to treatment discontinuation.

HPN-100-012 (Safety Extension)

Extent of Exposure

As of 01 March 2012, 22 UCD patients had enrolled into this ongoing, open-label safety study, including 15 who completed the switch over period of HPN-100-012 and 7 who enrolled

directly into the safety extension. The median exposure as of 01 March 2012 is approximately 3.5 month (range: 0.7 – 5.5 months).

This study of 22 patients 2 months to 5 years. There were no deaths or discontinuations due to AEs. There was no pattern of TEAEs or laboratory results suggesting any previously unknown toxicity of HPN-100. None of the children who were enrolled directly into the safety extension studied were started directly on HPN-100 without first being treated with NaPBA for control of their UCD. During this study, 16 patients have reported at least one TEAE. Most events were mild or moderate in intensity.

Three TEAEs were severe (Grade 3): hyperammonemia above 100 µmol/L (3 patients), and poor feeding. The most common TEAE was upper respiratory infection (7 patients), vomiting (3 patients), cough (4 patients), fever (3 patients), diarrhea (2 patients), and hyperammonemia (3 patients). No AEs led to treatment discontinuations.

HPN-100-011

As of March 1, 2012, there were 67 patients enrolled in this HPN-100 access program/ study. The most common TEAE was hyperammonemia in 11 (16.4%) patients, upper respiratory tract infection and vomiting, each occurring in 5 (7.5%) patients, and oropharyngeal pain in 4 (6.0%) patients. There were some SAEs: pancreatitis (1), hypokalemia (1), hyponatremia (1), convulsion (1) and hypocapnea (1). It is unclear if these events were related to drug. No AEs led to treatment discontinuations. Since these events occurred only once, it is hard to make an assessment of causality. 4% of patients in the long-term studies had convulsions, but these seizures/convulsions occur in patients with UCD because of chronic brain injury from recurrent hyperammonemic encephalopathy episodes.

HPN-100-008 Parts A and B (Hepatic Impairment studies)

150 patients were enrolled in this study. 5 hepatically impaired patients died, one of hepatic failure, two of gastrointestinal hemorrhage, two of acute renal failure. It is possible that the HPN-100 may have caused increased PAA toxicity, but this was not documented.

Gastrointestinal TEAEs were common in patients with hepatic impairment. Nausea, diarrhea and peripheral edema, all common in hepatically impaired patients occurred in approximately 10%. All together 33 patients have discontinued so far: 8 patients discontinued for AEs in this study; 10 patients met stopping rules, with events such as hemorrhage, renal failure, respiratory failure and sepsis; 3 patients underwent liver transplant, 2 had elevated INRs, ; 2 had low platelet counts; 2 patients had 10-fold elevations in ALT and AST; 4 patients with a variety of other lab disorders; 1 patient had a grade 4 neurological even (epilepsy); 1 patient had an increase in QTc > 60 msec over the morning value. The hepatically impaired population appeared to be more vulnerable to serious events such as gastrointestinal hemorrhage, renal failure, cirrhosis, hepatorenal syndrome, bacterial peritonitis, ascites and cirrhosis. It is not clear what the role of HPN-100 was in leading to discontinuation because the controlled part of the study (B) is still blinded. Because of the different adverse event profile of this patient population, it is unclear how instructive this study is for our understanding of safety in the UCD population.

9. Advisory Committee Meeting

An advisory committee meeting was not held because the active moiety is the same as the approved drug (therefore, Ravicti is not meet the definition of a new molecular entity), there were no safety concerns, and it met its primary efficacy endpoint.

10. Pediatrics

See Efficacy and Safety sections above for description of pediatric experience with Ravicti.

In a response to an information request to Hyperion Pharma, Inc., regarding DGIEP concerns that HPN-100 might not be properly absorbed into the blood stream from the intestines because of immature pancreatic exocrine function during the first 2 months of life, Hyperion stated that, “Measurements of fat absorption in newborns confirms that digestion of fat during early neonatal life varies widely, ranging from nil to nearly normal adult levels, and that the newborn’s ability to digest fats generally matures rapidly to normal adult levels during the first two months of life.⁴⁹” The article by Manson et al used a C-labeled mixed triglyceride (MTG) to show that neonates have a limited capacity to digest dietary fat and that a rapid maturation in intraluminal fat digestion during the early months of life. The publication also described the use of a stable isotope breath test (the MTG breath test) as a simple, reproducible, non-invasive way of measuring the development of fat digestion in early life.⁵⁰ There were other articles that provided evidence to support the neonatal deficiency of pancreatic exocrine function.

In a response to an information request on 12/7/12 regarding our concern, Hyperion responded as follows, reflecting their recognition of the concern of effectiveness and safety in the under 2 month population and their willingness to do further study:

“Although the data from protocol HPN-100-012 indicate that the gastrointestinal absorption of [phenylbutyrate] delivered as HPN-100 is at least equivalent to the absorption of PBA delivered as NaPBA down to two months of age, Hyperion agrees that there are no data yet available on HPN-100 digestion and PBA absorption during the first two months of life. Published data summarized below suggest that the efficiency of fat digestion and absorption in the neonate is variable and tends to mature over the first two months of life. Therefore, Hyperion shares the theoretical concern of the Division regarding administration of HPN-100 to neonates up to two months of age would be agreeable to add a warning to that effect in the label until prospective information can be collected in this age group. Hyperion would also be receptive to a post marketing requirement (PMR) to conduct a study in neonates up to two months of age and currently has plans to undertake such a study irrespective of a PMR.”

The review team agrees with Hyperion’s proposal to conduct a PMR in patients less than 2 months of age. However, we have been very clear in our communications with Hyperion that

⁴⁹ Manson WG et al, Development of fat digestion in infancy, Arch Dis child Fetal Neonatal Ed 1999;80:F183-F187.

⁵⁰ Boehn G et al, Biomed.Biochi. Acta 49 (1990) 5, 369-373.

we do not believe that the issue with the patients less than 2 months of age is purely a theoretical concern. There are published articles regarding the immaturity of pancreatic function in the neonate. Therefore, it is possible that the other lipases available to the neonate may not be sufficient to metabolize Ravicti into PBA and its glycerol backbone. If this were so, Ravicti would not be effective in the newborn. Therefore, a PMR is necessary as well as a contraindication against providing Ravicti to patients less than 2 months. The label will explain in the contraindication section that it is possible that infants less than 2 months of age will be able to metabolize Ravicti, but that this is yet to be demonstrated. Without evidence to support efficacy and safety in this population, the consequences of misjudging this situation are too grave. For this reason, a contraindication in the < 2 month old population with a PMR requiring study in this vulnerable period is required. The FDA Ethics Committee provided their concurrence with this approach.

For patients between 2 months and 2 years of age, there were only 4 patients enrolled. Insufficient information is available to recommend dosing in this patient population. Furthermore, two of the patients in this age range had elevated PAA levels in the 500 µg/mL range. Therefore, in the label, Ravicti will not be indicated for patients < 2 years of age. Safety and efficacy in this population has not been established. A PMR for this population to study PK/PD and safety has been proposed and accepted by the applicant. The trial will be a RCT in newly diagnosed patients who are mostly transitioning to oral nitrogen binders after stabilization on IV Ammonul. It will be acceptable to include some patients who have been on phenylbutyrate and who are transitioning to Ravicti.

11. Other Relevant Regulatory Issues

Financial Disclosures

The only research grant that caught my attention was one paid to Dr. (b) (6). He received \$39,762.00 to conduct an in (b) (6) study. (b) (6) enrolled (b) (6) out of a total of (b) (6) patients in (b) (6) and (b) (6) out of a total of (b) (6) patients in HPN (b) (6).

There were 33 investigators in the studies prior to HPN-100-012 and 7 investigators in Study HPN-100-012 who, according to Form 3454 did not enter into any financial arrangement with Hyperion whereby the value of compensation could affect the outcome of the study as defined in 21 CFR 54.2(a), did not have any proprietary interests in the product and were required to disclose if they did, and were not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

DSI Audits

No outstanding issues.

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Dr. Karen Malek from the Division of Good Clinical Practice Compliance stated the following in her review: “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.”

12. Labeling

REMS

FDA originally asked for a REMS but also informed Hyperion that if they submitted data for children between ages 29 days and 5 years, a REMS might not be needed. A consult by Dr. Choudhry from Division of Risk Management (DRISK) reviewed the proposed REMS for Ravicti that was submitted with the original application in response to a September 13, 2011 information request (IR) that consisted of:



The additional pediatric data (Study HPN-100-012) submitted as 120-day Safety in April 2012 was considered adequate by DGIEP for approval of Ravicti as adjunctive therapy for chronic management of UCD in pediatric patients ≥ 2 years of age. A decision was made by DRISK in conjunction with DGIEP and the REMS Oversight Committee (ROC) (email communication dated September 26, 2012) that a REMS for Ravicti is not necessary to ensure that benefits outweigh the risks of Ravicti treatment. After thorough review of the complete submission including the results of the pediatric study, HPN-100-012, it was concluded that the risks associated with treatment of Ravicti can be managed through labeling, routine pharmacovigilance, a non-REMS Medication guide which will explain the limitations of use of Ravicti and provide administration guidance. There will also be several PMRs (see introduction and recommendation/risk benefit section).

Proprietary Name

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Carlos Mena-Grillasca RPH of Division of Medication Error Prevention and Analysis (DMEPA) concluded in his review that the proprietary name, Ravicti, was acceptable as of November 29, 2012.

Package Labeling

DMEPA recommendations were as follows:

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.

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.

Carton Labeling

1. See comments from ***Container Labels (All Sizes)*** 3 and 4.
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 mLs 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.

Pregnancy Labeling

The applicant proposed labeling as Category C.

These recommendations were communicated to Hyperion and they have agreed to make the appropriate modifications to the label and carton and container labeling.

13. Recommendations/Risk Benefit Assessment

My recommendation, along with that of the review team, is for approval of HPN-100 for chronic management of UCDs in patients ≥ 2 years of age whose disorder is not controlled

with dietary management, amino acid supplementation alone or carnitine if indicated because of the favorable benefit-risk analysis of this nitrogen binding therapy. HPN-100, an orphan designated drug for the UCD indication, is as effective as its competing product, Buphenyl for controlling serum ammonia over a 24 hour period. This was demonstrated in one adequate and well-controlled, non-inferiority design study in adults with UCDs using a biomarker endpoint (serum ammonia AUC₀₋₂₄) which was agreed upon in an SPA. Serum ammonia is used to guide therapy of patients with UCDs and there are data analyses showing that venous blood ammonia levels correlate with clinical outcome (Batshaw, 1984;⁵¹ Enns, 2007;⁵² Logan, 1984.)⁵³ There were confirmatory findings from other uncontrolled studies in children down to age 2 years of age and long-term studies that demonstrated maintenance of ammonia control. There is clinical evidence that is supportive. The patients had slightly fewer episodes of hyperammonemic crisis during the long-term efficacy studies with HPN-100 than they had the year before when they were on Buphenyl (difference not statistically significant). Since the long-term studies were uncontrolled and the patients were enrolled in a study which may have improved dietary and medication compliance, this evidence (fewer hyperammonemia crisis cases) is not terribly compelling. However, it is reassuring to note that HPN-100 was successful at preventing hyperammonemic crisis in most UCD patients, a finding that would be unexpected in the absence of effective therapy. Furthermore, HPN-100 is not a new molecular entity because it has the same active moiety (PBA) as 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 mechanism of action of NaPBA is well understood and was able to control serum ammonia in most of the patients with UCDs who were studied. There are also certain characteristics of HPN-100-006 that make this single study adequate to support an effectiveness claim: It 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 the noninferiority results fell well within the margin of noninferiority.

There was an adequate safety data base including year long data in most patients except for patients less than 2 years of age; 268 subjects who received at least one dose of HPN-100; 112 UCD patients (65 adults, 26 children between the ages of 6 and 17 years and 22 patients < 6 years old) with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH across five studies (UP 1204-003, HPN-100-005, HPN-100-006, HPN-100-007, and HPN-100-012SE). 77 patients with UCDs had completed 12 months of HPN-100 at the time of the NDA submission. There were no deaths, few withdrawals, few SAEs and multiple mild to moderate nonserious AEs that could partly be due to the patients' underlying diseases. Considering the absence of other superior treatments for the chronic management of UCDs the safety profile is acceptable. At least for the 2 week controlled study in adults, the safety profile of Ravicti was not notably different from that of Buphenyl.

⁵¹ Batshaw ML. Hyperammonemia. *Curr Probl Pediatr* 1984;14(11):1-69

⁵² Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *New Engl J Med*. 2007; 356:2282-92.

⁵³ Logan WJ. Neonatal hyperammonemic encephalopathy. In: Sarnat HB, editor. *Topics in neonatal neurology* 1984. p. 137-57.

On a reassuring note, the levels of the toxic metabolite, PAA, were no higher when UCD patients were taking HPN-100 than when they were on the active control, Buphenyl.

The major benefit of Ravicti is that when given along with dietary management, it controls ammonia levels as well as the currently marketed product, Buphenyl in the patient populations in which it was well-studied, stable children > 2 years of age and adults. Since it has the same active moiety as Buphenyl, as long as there is adequate pancreatic exocrine activity, there should be no disadvantage to this preparation. It is a titratable product and patients are generally followed closely, so the absence of sufficient dose/ ammonia/ PAA data for PK modeling and dose extrapolation for this subpopulation is not a great concern. In the clinical studies, the safety profile of Ravicti appeared to be no worse than the safety profile for Buphenyl.

The deficiencies of the application, enumerated below, and also explained in the introduction, 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 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

The review team is going to request a delay for the final protocol submission as it may take longer to agree on the details of the protocol.

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

2. Very few data on patients in the age category of 2 months to 2 years were included in the NDA. The numbers of patients in this age range (4) and the timing of assessments

were insufficient to conduct an adequate exploration of an effective dosing algorithm (by mg/kg vs. mg/m²) and the association between adverse events and Ravicti metabolite (in particular, PAA) levels. Two of the four patients in this age-range had PAA levels ~ 500 µg/mL when on Buphenyl or HPN-100 which may be associated with neurotoxicity.

PAA toxicity, with neurological and gastrointestinal manifestations has been demonstrated with IV administration of PAA. The symptoms at PPA levels of ~500 µg/mL were somnolence, emesis and lethargy and were observed in patients with cancer who received IV PAA. More severe toxicity (confusion and psychomotor depression) occurred in patients with mean peak PAA level of 682 µg/mL⁵⁴. Overdose of IV PAA in children has been reported to cause coma and death.⁵⁵ Levels of PAA in the children who had coma or died were > 1000 µg/mL.

In addition to a neurotoxicity signal, there is also an animal carcinogenicity signal (see Pharmacology-Toxicology section). For these reasons, it is important to understand the safety and efficacy of HPN-100 in this patient population.

Recommendation: The clinical pharmacology review states that it is not possible from data provided in this NDA to provide safe and effective dosing instructions for patients < 2 years of age. Therefore, it is advisable to change the indication so that Ravicti is approved for patients with UCDs ≥2 years of age. Two PMRs in children between 2 months and 2 years of age were proposed to Hyperion and accepted. Hyperion agreed to commit to this PMR as worded below.

FDA Proposed PMR Language: Study in pediatric patients aged 2 months to 2 years with Urea Cycle Disorders. Patients when they are no longer in the acute hyperammonemic phase will be started on Ravicti. Ammonia levels and phenylacetic acid (PAA) levels will be checked on a fixed schedule and at the time of adverse events.

The FDA Proposed Language for the second PMR: Conduct pharmacokinetics studies in pediatric patients from birth to less than 2 years of age with Urea Cycle Disorders. PK of glycerol phenylbutyrate and its metabolites (PBA, PAA and PAGN) must be characterized.

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission for both PMRs: April 1, 2013

Study Completion Date: April 1, 2016 for the overall study and April 1, 2017 for the PK study

Final Report Submission for the overall study: December 1, 2016 and December 1, 2017 for the PK study.

⁵⁴ Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. Cancer 1995;75:2932-8.

⁵⁵ Parphanphoj et al (2000), Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring after the treatment of acute hyperammonemia, J. Inherit. Metab. Dis 23: 129-36.

The review team is going to request a delay for the final protocol submissions as it may take longer to agree on the details of the protocol.

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

3. In clinical studies in support of NDA203284 most patients were on an established dose of Buphenyl (sodium phenylbutyrate) prior to enrolling in the trial. The dose of Ravicti administered to most patients was determined by a formula used to provide equal dose of phenylbutyrate (PBA) as they had been receiving from Buphenyl, sodium PBA. Therefore there is limited experience with dosing of Ravicti in treatment naïve patients. A concerning safety signal was that 2 of the 6 patients who were started on Ravicti without first attaining a stable dose of Buphenyl had neurological TEAEs that lead to dose reduction and discontinuation. Ravicti has the same active moiety as Buphenyl. Therefore, it is considered safe for the purpose of approval to initiate dosing with Ravicti. However, the signal of neurotoxicity that was seen in the 2 patients who were not already stabilized on Buphenyl raises the concern that treatment naïve patients may not tolerate de novo dosing with this product as well as they do with Buphenyl.

Recommendation: The review team has agreed that dosing instructions in the label will have to be divided into several sections as follows:

2.1 Important Instructions

RAVICTI should be prescribed by a physician experienced in the management of UCDs. Instruct patients to take RAVICTI with food and to administer directly into the mouth via oral syringe or dosing cup. See the instructions on the use of RAVICTI by nasogastric tube or g-tube [see *Dosage and Administration (2.6)*].

The recommended dosages for patients switching from sodium phenylbutyrate to RAVICTI and patients naïve to phenylbutyric acid are different [see *Dosage and Administration (2.2, 2.3)*]. For both subpopulations:

- Give RAVICTI in three equally divided dosages, each rounded up to the nearest 0.5 mL
- The maximum total daily dosage is 17.5 mL (19 g)
- 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).

2.2 Switching from Sodium Phenylbutyrate to RAVICTI

Patients switching from sodium phenylbutyrate to RAVICTI should receive the dosage of RAVICTI that contains the same amount of phenylbutyric acid. The conversion is as follows:

Total daily dosage of RAVICTI (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.8

2.3 Initial Dosage in Phenylbutyrate Naïve Patients

The recommended dosage range, based upon body surface area, in patients naïve to phenylbutyrate (PBA) is 4.5 to 11.2 mL/m²/day (5 to 12.4 g/m²/day). For patients with some residual enzyme activity who are not adequately controlled with protein restriction, the recommended starting dosage is 4.5 mL/m²/day.

In determining the starting dosage of RAVICTI in treatment naïve patients, consider the patient's residual urea synthetic capacity, dietary protein requirements, and diet adherence. Given that approximately 47% of dietary nitrogen is excreted as waste and 70% of an administered PBA dose will be converted to urinary phenylacetylglutamine (U-PAGN), an initial estimated RAVICTI dose for a 24 hour period is 0.6 mL RAVICTI per gram of dietary protein in 24 hours.

2.4 Dosage Adjustment and Monitoring

Adjustment based on Plasma Ammonia: Adjust the RAVICTI dosage to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) (according to age).

Adjustment based on Urinary Phenylacetylglutamine: If available, U-PAGN measurements may be used to help guide RAVICTI dose adjustment. Each gram of U-PAGN excreted over 24 hours covers waste nitrogen generated from 1.4 gram of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dose should be adjusted upward. Consider a patient's use of concomitant medications, such as probenecid, when making dosage adjustment decisions based on U-PAGN. Probenecid may result in a decrease of the urinary excretion of PAGN [see *Drug Interactions (7.2)*].

Adjustment based on Plasma Phenylacetate: If available, measurements of the plasma PAA levels may be useful to guide dosing if symptoms of vomiting, nausea, headache, somnolence, confusion or sleepiness are present in the absence of high ammonia or intercurrent illness. Ammonia levels must be monitored closely when changing the dose of RAVICTI [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

2.5 Dosage Modifications in Patients with Hepatic Impairment

For patients with moderate to severe hepatic impairment the recommended starting dosage is at the lower end of the range [see *Warnings and Precautions (5.1, 5.4)* and *Clinical Pharmacology (12.3)*].

2.6 Preparation for Nasogastric Tube or Gastrostomy tube Administration

For patients who have a nasogastric tube or gastrostomy tube in place, administer RAVICTI as follows:

- Utilize an oral syringe to withdraw the prescribed dosage of RAVICTI from the bottle.
- Place the tip of the syringe into to the tip of the g-tube/nasogastric tube

- Utilizing the plunger of the syringe, administer RAVICTI into the tube.
- Flush once with 30 mL of water and allow the flush to drain.
- Flush a second time with an additional 30 mL of water to clear the tube.

To address the concerns that initial dosing and titration based on the instructions from the label may not be safe and effective, a PMR has been stipulated and Hyperion has agreed to fulfill it.

The FDA proposed language for the PMR was as follows: Randomized controlled clinical trial to assess the safety and efficacy of initiating and titrating Ravicti in treatment naïve patients with UCDS

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission: December 1, 2013

Study Completion Date: June 1, 2016

Final Report Submission: March 30, 2017

We are awaiting agreement from the Safety Review Team, SWAT and Office of Chief Counsel.

4. Inconclusive Thorough QT (TQT) study

Recommendation: The IRT-QT recommended that a repeat study should be performed because of lack of assay sensitivity in the original study or there should be language in the label to explain the lack of assay sensitivity. For there to be assay sensitivity, the moxifloxacin effect on QT interval must show an upslope from normal to elevated. This upslope was not demonstrated. The QT interval was high from the first ½ hour which was the first data point captured in the report. Additionally, the moxifloxacin effect on QT was 10 ms at first but then declined to 10 ms and stayed there. This is not usual. Ravicti did not show any prolongation of QT interval and because there was no upslope and because there was no great variability, the IRT-QT team stated that even with absence of assay sensitivity, it is unlikely that Ravicti prolongs the QT interval ≥ 10 msec. The review team agreed with the IRT-QT team's recommendation and proposed language to the applicant for use in the QT section of the label:

The effect of multiple doses of Ravicti 13.2 g/day and 19.8 g/day (approximately 69% and 104% of the maximum recommended daily dosage) 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. However, assay sensitivity was not established in this study. Therefore, an increase in mean QTc interval of 10 ms cannot be ruled out.

The applicant was informed that they will need to repeat a thorough QT study with assay sensitivity or they will need to demonstrate that there was an upslope in the moxifloxacin arm from a normal length to a prolonged length to have this language removed from the label.

5. The risks of treating breast-feeding patients are not known. There is a concern of effects on unborn fetuses and neonates because of neurotoxicity findings seen with Buphenyl in rat pups given HPN-100 in their food, and carcinogenicity findings in a 2-year rat carcinogenicity study which the Cancer Assessment Committee deemed as being drug-related. It is unknown if PBA, PAA, or PAGN pass into the breast milk. Ravicti is expected to be used by women of reproductive age and data on exposure of the drug via breast milk is needed.

Recommendation: Appropriate language will be placed in the label for pregnant and breast-feeding patients and encouragement to participate in the Ravicti Urea Cycle Disorders registry. We are in the process of having the PMHS team consult to help provide the appropriate language in the label. PMHS is also being asked to advise the applicant about conducting an appropriately designed post-marketing study to assess the quantity of PBA, PAA, or PAGN that passes into breast milk.

6. CYP enzyme interactions. 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.

Recommendation: Since chronic administration of Ravicti is expected for UCD patients, the evaluation of the potential in vivo drug interaction with concomitant medications that may compete for CYP enzymes is warranted.

The FDA proposed language for the PMR: In vivo drug interaction study to evaluate the effect of Ravicti on the pharmacokinetics of a drug that is a sensitive substrate of CYP3A4/5 (e.g., midazolam).

The timetable submitted by Hyperion for this study is as follows:

Final Protocol Submission: September 30, 2013

Study Completion Date: March 31, 2014

Final Report Submission: July 1, 2014

7. Patients with advanced hepatic disease had elevated phenylacetate (PAA)/Phenylacetylglutamine (PAGN) ratios because they do not convert PAA to PAGN as quickly as a person without advanced hepatic disease. Patients with advanced hepatic impairment are therefore at risk of developing PAA toxicity. There were 5 patients in the hepatic impairment studies who died. Their deaths may have been related to their underlying disease. PAA toxicity was not evaluated in these patients. 2 were known to be on HPN-100, the 3 others were in an ongoing study (HPN-100-008 Part B) that is still blinded.

Recommendation: Labeling in the Dosage and Administration Section (2.4) and in the Special Populations Section 8.6 will be placed to advise practitioners to start patients

with hepatic disease at the lower end of the dosing range. There will also be a warning in the Warnings and Precautions in Section 5.5 for patients with advanced hepatic disease explaining that they are at increased risk for PAA toxicity.

8. There are unknown benefits and risk of treating patients with renal disease.

Recommendation: In section 12.3 Pharmacokinetics the following language has been proposed to Hyperion:

Renal Impairment

The pharmacokinetics of Ravicti in patients with impaired renal function including end-stage renal disease (ESRD) or on hemodialysis have not been studied.

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

/s/

MELANIE J BLANK
01/31/2013