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MEDICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name Ravicti

Therapeutic Class Not established
Applicant Hyperion Therapeutics

Formulation(s) Liquid
Dosing Regimen TID with meals
Indication(s) Adjunctive therapy for chronic
management of patients with
Urea Cycle Disorders
Intended Population(s) Pediatric and adult patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of this application is recommended. The population studied in the Ravicti clinical development program, patients with Urea Cycle Disorders (UCD) aged 29 days and older, requires life-long treatment for this rare and life-threatening condition. Since 1996 treatment has been available for chronic management in the form of sodium phenylbutyrate (Buphenyl®). Ravicti was found to be non-inferior to Buphenyl in a single Phase 3 study of UCD patients with deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase deficiency (OTC), or argininosuccinate (ASS). In a small cross-over study fifteen pediatric patients age 29 days to 6 years were switched from Buphenyl to Ravicti and followed for ten days.

1.2 Risk Benefit Assessment

The risk-benefit assessment supports approval of Ravicti based on the following considerations:

Risks - A 2-year study to assess the carcinogenic potential of HPN-100 was conducted in male and female Sprague-Dawley rats. The rat carcinogenicity study showed an increased incidence of tumors of the pancreas, thyroid, adrenal cortex, uterus, Zymbal's glands, and cervix. Because Buphenyl and Ravicti share the same active moiety these findings would pertain to Buphenyl as well. No carcinogenicity studies were submitted with the Buphenyl application. A search by the FDA Division of Pharmacovigilance for reports in the adverse events reporting system (AERS), or literature reports of neoplasms in UCD patients taking Buphenyl did not yield any cases.

A second potential risk of Ravicti is toxicity of the active metabolite phenylacetic acid (PAA). PAA toxicity has been reported in UCD and non-UCD patients receiving intravenous sodium benzoate and sodium phenylacetate. In studies conducted for the Ravicti application adverse events in UCD patients suggestive of PAA toxicity were not seen. However in some studies PAA levels were not obtained, either because blood samples could not be drawn or because obtaining PAA levels was not part of the study protocol. In adult UCD patients PAA levels were lower with Ravicti than NaPBA. PAA levels were higher in pediatric patients than adults for both Ravicti and Buphenyl.

Dosing of Ravicti was based on the dose of Buphenyl the patient was receiving at baseline, and in cross-over studies doses were not titrated. Although patients in the Phase 3 safety and efficacy trial had similar outcomes whether receiving Ravicti or Buphenyl, this trial did not enroll pediatric patients. In a small pediatric study of UCD patients under the age of 6, only four patients were less than two years of age, and one less than 12 months. Overall, there is a paucity of data available in pediatric patients

upon which to base dosing to control ammonia levels while also maintaining safe levels of the metabolite phenylacetic acid.

Benefits – If approved, Ravicti will be the second nitrogen scavenging drug to be available, in conjunction with diet, for chronic management of UCDs. In the clinical studies in UCD patients there were no deaths. The overall adverse event (AE) profile was similar to that of NaPBA, and AEs tended to diminish over time. Ravicti was able to control ammonia levels as well as NaPBA, and also reduce glutamine levels.

Ravicti has further benefits with respect to formulation palatability and sodium load. For patients of the ASL subtype, who are genetically prone to hypertension, the high sodium content of Buphenyl is problematic. In contrast, Ravicti is sodium free. In addition the taste and odor of Ravicti is more neutral, and the pill burden and volume of liquid associated with drug administration is less.

In the final analysis, UCDs are rare diseases, and patients require life-long treatment for their condition. Although Ravicti is not risk-free, the risks that have been identified with Ravicti would pertain to Buphenyl as well. The benefits and ease of use outweigh the risks associated with this drug.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This reviewer does not recommend that a postmarket risk evaluation and mitigation strategy (REMS) be implemented. At the time of the NDA submission data on pediatric patients less than six years of age were not available. In order to limit access to Ravicti only to patients six years of age and older the company submitted a REMS. In April 2012 the sponsor completed study HPN-100-012, which studied pediatric patients down to ≥ 29 days. As is discussed later in this review, fifteen patients aged >29 days to six years were successfully switched from Buphenyl to Ravicti. Although the number of patients is small, it is acceptable for this rare disease, whose prevalence is <2000 patients. Ravicti was found to work as well as Buphenyl in controlling serum ammonia levels in this patient population, with few adverse events reported. Study HPN-100-012 provided efficacy and safety data for Ravicti that had previously been missing, and obviates the need for REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

Two postmarketing studies are recommended:

- A PK and safety study in pediatric patients under the age of two years to better inform dosing in this age group.
- A repeat thorough QT (tQT) study to assess the cardiovascular safety of Ravicti in which assay sensitivity is demonstrated.

2 Introduction and Regulatory Background

Urea Cycle Disorders

Urea Cycle Disorders (UCDs) are rare genetic disorders resulting from deficiencies of the following enzymes or transporters: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase (CPS), ornithine transcarbamylase 1 (OTC 1), argininosuccinate synthetase (AS or ASS), argininosuccinate lyase (AL or ASL), arginase (ARG). These disorders prevent the normal conversion of waste nitrogen into urea, and result in the accumulation of toxic levels of ammonia in the blood and brain of affected patients.

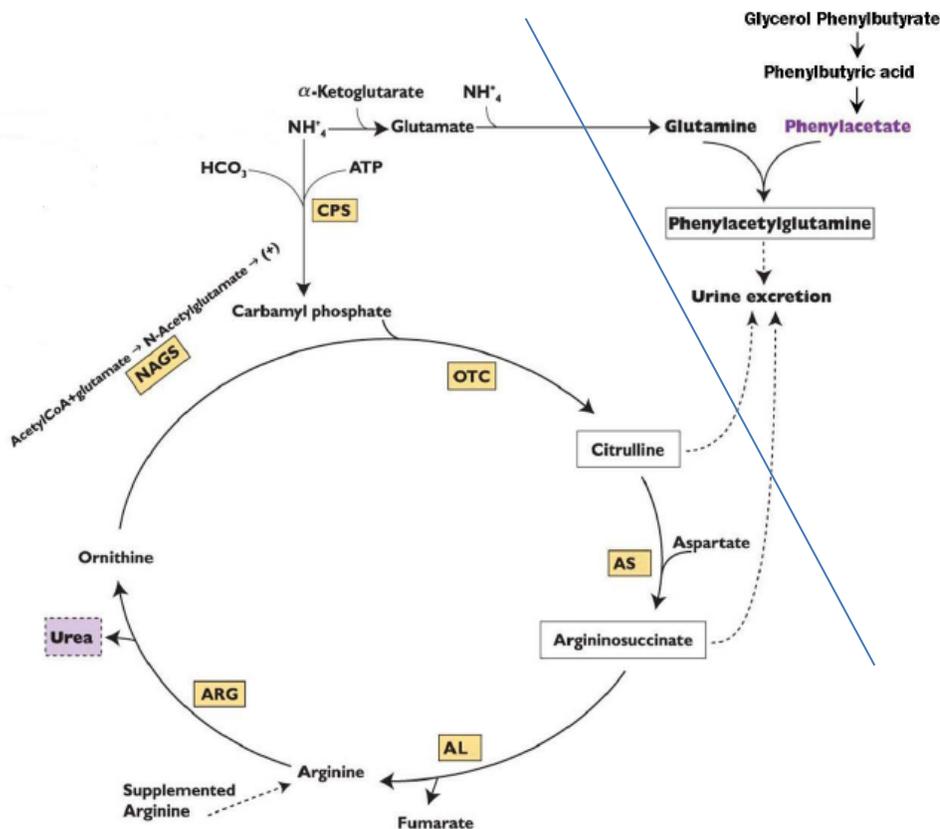
The clinical manifestations of UCDs are due to hyperammonemia, and management is based on controlling ammonia levels and avoiding a hyperammonemic crisis. Some patients have a total or near total absence of activity of the first four enzymes of the urea cycle (CPS, OTC, AS, AL) and accumulate ammonia and other precursor metabolites during the first few days of life. Other patients may have a milder form of the disease. In the second group hyperammonemia is less severe, and symptoms more subtle than in patients with early-onset disease.¹

Treatments are aimed at reducing ureagenesis through dietary protein restriction, arginine or citrulline supplementation (which can enhance waste nitrogen excretion in patients with ASS and ASL subtypes), and administration of nitrogen-scavenging drugs. Currently approved nitrogen scavenging drugs include sodium phenylbutyrate (BUPHENYL®) tablets or powder for chronic management of UCDs, and intravenous sodium phenylacetate with sodium benzoate (AMMONUL®) for acute management of hyperammonemia.

The following Figure 1 depicts the alternative pathway for nitrogen disposal in lieu of the urea cycle. The large circle at the center shows the site at which each enzyme functions in patients without urea cycle disorders. The pathway on the right bypasses the urea cycle, and provides patients lacking in critical UCD enzymes an alternate pathway by which to dispose of nitrogen.

¹ Summar ML, Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicenter study of acute hyperammonemic episodes. *Acta Paediatrica* 2008; 97:1420.

Figure 1 Alternate Pathway for Nitrogen Disposal



[Ref: HPN-100-007 Clinical Study Report, Figure 1, p.17]

Glycerol phenylbutyrate (Ravicti) is a pre prodrug that contains 3 moles of phenylbutyric acid (PBA) joined to glycerol in an ester linkage. In the small intestine it is hydrolyzed by pancreatic lipases to PBA, and then follows the same chemical pathway as Buphenyl. Results of an in vitro study of pancreatic lipase activity against HPN-100 conducted during Ravicti development showed that pancreatic triglyceride lipase (PTL), carboxyl ester lipase (CEL) and pancreatic lipase related protein 2 (PLRP2) all hydrolyzed HPN-100. This is important because even though PTL is absent in the early neonatal period, PLRP2 and CEL may contribute to digestion of HPN-100 until the appearance of PTL. [Ref: Digestive Lipases Activity on HPN-100]

The rationale for developing HPN-100 (Ravicti) is that it lacks the high pill burden, odor, bad taste, and high sodium content (~2300 mg/d for patients taking 20 g Buphenyl) associated with Buphenyl. Removing these impediments may increase compliance, and decrease hyperammonemic episodes.

Reviewer's Comment:

In the NDA review the names Ravicti, HPN-100, and glycerol phenylbutyrate are used interchangeably. All are the to-be-marketed drug product. Likewise the currently approved drug Buphenyl is also referred to as NaPBA, or sodium phenylbutyrate.

2.1 Product Information

Established name: Glycerol Phenylbutyrate

Proposed Trade Name: Ravicti

Chemical Class: Ester

Pharmacological class:

Ravicti is a triglyceride with three molecules of phenylbutyrate (PBA) joined via an ester linkage to a glycerol backbone. It is a prodrug of PBA and a pre-prodrug of phenylacetate (PAA), the active moiety of the compound. The pharmacotherapeutic group is expected to be alimentary tract and metabolism product.

Proposed Indications:

The proposed indication for Ravicti is adjunctive therapy for chronic management of adult and pediatric patients (b) (4) with urea cycle disorders involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (hyperornithinemia–hyperammonemia–homocitrullinuria [HHH] syndrome, also referred to as ornithine translocase deficiency).

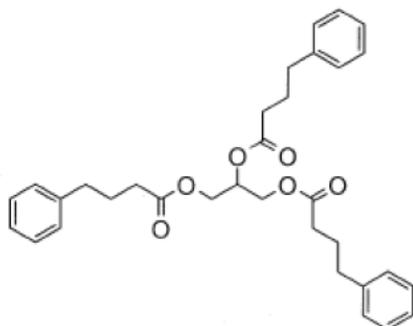
Dosing Regimen:

The sponsor's recommended starting dose is based on body surface area (BSA). For patients with a BSA (b) (4)

The recommended dosing range for (b) (4) adult UCD patients is 4.5 mL/m²/day to 11.2 mL/m²/day [5.0 g/m²/day to 12.4 g/m²/day]; with the total daily dose not to exceed 17.5 mL [19g]).

Figure 2 Structural Formula

Structural formula:



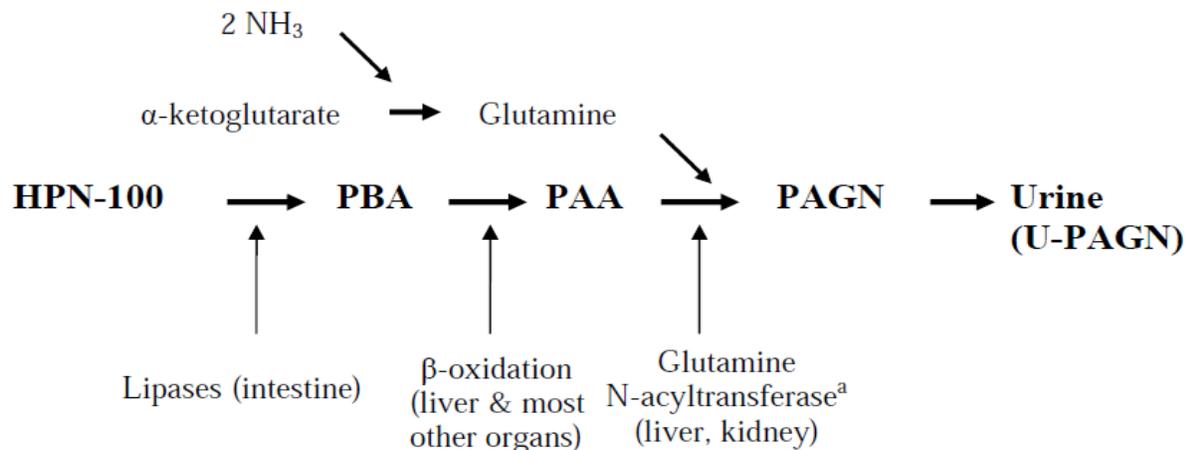
Molecular formula: $C_{33}H_{38}O_6$

Relative Molecular Mass: 530.67

The drug product is composed of (b) (4) a clear colorless to pale yellow liquid, filled into glass bottles. There are (b) (4).

After oral administration glycerol phenylbutyrate is hydrolyzed to phenylbutyrate (PBA) in the gastrointestinal tract by intestinal lipases. Intact HPN-100 is not detected in the circulation. Phenylbutyrate undergoes β -oxidation to the active metabolite, phenylacetate (PAA). PAA is conjugated with glutamine via acetylation in the liver and kidney to form phenylacetylglutamine, and excreted in the urine as U-PAGN. Glutamine levels correlate with plasma ammonia; elevated levels of glutamine can result in accumulation of glutamine in glial cells, and cause cerebral edema. The nitrogen content of PAGN per mole is identical to urea (both contain 2 moles of nitrogen). The metabolic pathway for HPN-100 is shown below in Figure 3.

Figure 3 Metabolic Pathway of HPN-100



[Ref: Clinical Overview, Figure 2.5-1, p.13]

2.2 Tables of Currently Available Treatments for Proposed Indication

Urea Cycle Disorders are managed chronically and acutely. Ravicti is proposed for chronic use. Buphenyl is the only drug currently marketed in the US for the same chronic indication. Buphenyl comes in a tablet or powder form. Once broken down chemically, Buphenyl and Ravicti have the same active moiety, phenyl acetic acid.

Table 1 Currently Available Treatment for Proposed Indication

Drug	Formulation	Indication	Dosage
NaPBA (Buphenyl®) NDA20572	tablet (500mg)	chronic management	<20 kg - 450-600 mg/kg/day >20 kg – 9.9-13g/m ² /day
NaPBA (Buphenyl®) NDA20573	powder	chronic management	<20 kg - 450-600 mg/kg/day >20 kg – 9.9-13g/m ² /day

[Ref: Buphenyl prescribing information]

Ammonul is another nitrogen scavenging drug, but its indication differs from that of Buphenyl and Ravicti in that it is used as an intravenous formulation for acute management of hyperammonemia.

Reviewer's Comment:

The Buphenyl label offers a dosing range based on weight in kilograms. Much discretion is left to the prescribing physician.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient glycerol phenylbutyrate is not available in the United States since it is not yet approved.

2.4 Important Safety Issues with Consideration to Related Drugs

Buphenyl was approved in 1996 by the Division of Metabolism and Endocrine Drug Products. Approval was based on a review of clinical data from Dr. Saul Brusilow in

pediatric patients in whom serum ammonia was managed with NaPBA and diet. The study was non-randomized and uncontrolled, and no formal PK study was done in pediatric patients. No animal safety data were provided, and pre-clinical carcinogenicity and pharmacokinetic studies were not performed. The Annual Periodic Safety reports for Buphenyl covering the period May 1, 2009 to April 30, 2010, and May 1, 2010 to April 30, 2011 did not reveal any new safety signals or reports of neurologic adverse events.

However, as will be discussed further in this review, there have been literature reports from the 1980's and 1990's of possible safety issues associated with the active metabolite phenylacetic acid (PAA). Phenylacetate has been associated with nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, dizziness, slurred speech, memory loss, confusion, and disorientation at PAA levels ranging from 499-1285 µg/mL². These adverse events resolved with discontinuation of the drug. Cases have also been reported of toxicity from intravenous sodium benzoate and sodium phenylacetate when administered for the treatment of acute hyperammonemia.³ The clinical manifestations of PAA toxicity (headache and vomiting) may mimic those of hyperammonemia. In UCD patients in studies conducted for this NDA PAA levels were not associated with neurologic adverse events.

Reviewer's Comment:

In both references patients were receiving intravenous treatment. PAA levels should be monitored, particularly when ammonia levels decrease but neurologic symptoms do not.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Orphan Drug Designation was given for this indication on 5-May-2006 (#05-2035). The sponsor was granted fast-track designation 4-Oct-2010. The sponsor and the Agency reached agreement on a Special Protocol Assessment for Phase 3 protocol HPN-100-006 on 6-July-09. Below is a brief discussion of meetings with FDA.

PIND73480 meeting 12-Dec-05

At this meeting it was agreed that GT4P (later changed to HPN-100) was not a new molecular entity. Because PK studies showed that GT4P is not bioequivalent (plasma and urinary excretion lower) to Buphenyl a clinical trial is needed. Pre-clinical data showed the potential to prolong the QT interval, so a tQT study was required.

² Thibault A, et al. A Phase 1 and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer. *Cancer Research* 54: 1690-1694, 1994.

³ Praphanphoj, V. Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonemia. *J. Inherit. Metab. Dis* 23:129-135.

Type C meeting 17-March-08

Among the issues discussed at this meeting were the transition of patients from Buphenyl to HPN-100, and the need for the company to review Phase 1 data prior to embarking on pediatric studies.

Type B meeting 14-Jan-09

The objective of this meeting was to gain agreement on the design of Phase 3 trials. The sponsor was advised that only UCD subtypes studied could be indicated in the labeling. Measurement of ammonia AUC and plasma phenylacetylglutamine (PAGN) AUC should be included as co-primary efficacy measures (AUC since it will provide a better estimate of overall effect rather than at a certain time point). Two additional blood ammonia samples were added between 12 and 24 hours, and cross-over design deemed acceptable. A long term extension study will be required for chronic use. The FDA advised the sponsor that a pediatric study should be completed prior to the pivotal efficacy study to properly inform the design of the pivotal trial that will include pediatric patients. The sponsor has applied for orphan designation.

Type A meeting 7-May-09

This meeting was requested since the company and FDA failed to reach agreement on a SPA protocol. FDA recommended that the company use 1.25 as the upper confidence limit (ratio of NH₃ 24 hour AUC values).

FDA CMC Advice Letter 17-Sept-10

The purpose of this meeting was to address questions concerning process validation.

CMC pre-NDA meeting 8-Dec-10

The purpose of this meeting was to address questions concerning impurity limits.

Type B Pre-NDA 7-Dec-10

The agency expressed concern with results of HPN-100-005, a Phase 2 study in which treatment with HPN-100 (b) (4) formulation resulted in a 90% higher PAA exposure than treatment with NaPBA, in pediatric patients. Therefore FDA required a clinical trial evaluating dosing and safety in pediatric patients. FDA recommended studying doses in pediatric patients that would provide comparable systemic exposure to PBA and PAA to those in adults. As noted in the meeting discussion, specific review issues are likely to include dosing in patients less than 6 years of age and better understanding of the PAA levels in patients 6-17 years of age.

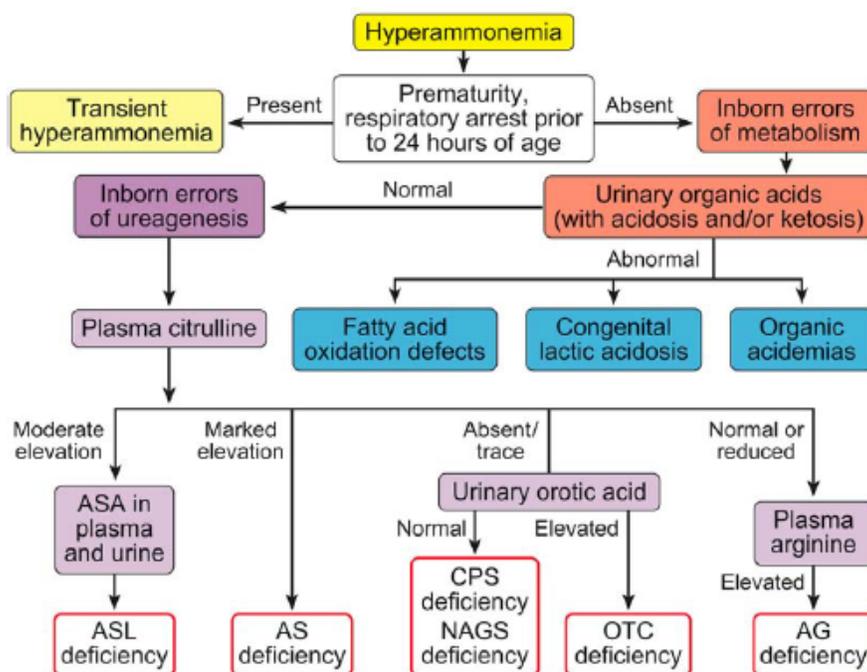
2.6 Other Relevant Background Information

Most patients with UCDs are diagnosed after presenting with symptoms of hyperammonemia. Severe (e.g., seizures, cerebral edema, hyperventilation, posturing, coma) and less severe (e.g., loss of appetite, headache, cyclical vomiting, lethargy, behavioral abnormalities, sleep disorders, delusions, hallucinations, psychosis, headaches, GI symptoms including nausea and vomiting) manifestations can be nonspecific, resulting in long delays between the initial onset of symptoms and

diagnosis. Certain manifestations of hyperammonemia (e.g., headache, vomiting) also may mimic those reportedly associated with elevated levels of PAA.

If an elevated blood ammonia level is confirmed and results of other routine laboratory tests are consistent with a UCD diagnosis (e.g., normal anion gap, normal blood glucose, absence of liver disease), amino acid levels are tested to establish a specific diagnosis. UCD diagnoses may be confirmed with enzymatic or genetic testing, although amino acid abnormalities may be sufficient. Treatment should be initiated as early as possible to minimize the risk of death or neurologic damage. The following flowchart illustrates the approach to evaluating hyperammonemia in newborns.

Figure 4 Approaches to Hyperammonemia



[Ref: ISE, Figure 2.7.3-8, p.28, (Adapted from Summar, 2001b)]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted electronically on 23-DEC-2011. On 20-APR-2012 the applicant submitted the results of pediatric study HPN-100-012. Because these data were submitted separately it was left to the reviewer to attempt to integrate the two data sources. The pediatric data were critical to the review because of the need to have reliable dosing and safety information in this patient population. Receiving these two

separate submissions at different times detracted from the overall quality of the application.

A response to an information request (IR) was received from the sponsor late in the review cycle, and resulted in a need to extend the review clock. The clinical data requested in the IR was for PAA and ammonia levels at the time a patient experienced neurologic adverse events, or nausea and vomiting. These were adverse events of interest because neurologic adverse events or nausea and vomiting can be a sign of either hyperammonemia or PAA toxicity.

The basic organization of the application was otherwise acceptable.

3.2 Compliance with Good Clinical Practices

Inspections of three clinical sites were done by the FDA Division of Good Clinical Practice Compliance, Office of Scientific Investigations. These sites were chosen because they enrolled 50% or more of the patient population. The investigators chosen for inspection participated in three protocols: UP1204-003, HPN-100-005, and HPN-100-006. Two investigators/sites received a VAI (deviations(s) from regulations), and one received an NAI (no deviation from regulations). There were no violations relating to informed consent or ethical standards in conduct of the trials.

Among the violations at one site were failures to report the adverse events of bloating, headache and papular lesions on the chest and back (diagnosed as Herpes Zoster). Another violation was that none of the study subjects were switched over gradually to the 100% HPN-100 treatment. These violations do not affect the validity of the data.

At a second site there were two protocol violations. One was failure to report the serious adverse reaction of pre-dose ammonia of 161 within 24 hours, as required by the protocol. A second violation in the long-term safety extension study was failure to obtain spot PK and urine analysis at a 3 and 5 month visits for two separate patients. The IRB subsequently removed this requirement.

Reviewer's Comment:

Overall none of the violations compromise the integrity of the data or the study, and the application is in compliance with good clinical practices. It is regrettable that pediatric study HPN-100-012 was not completed at the time of NDA submission since an inspection of sites involved with this study would have been desirable. Importantly, however, sites from pivotal Phase 3 study HPN-100-006 were part of the OSI inspection process.

3.3 Financial Disclosures

The sponsor has certified that the clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of the compensation to the investigator could be affected by the outcome.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In his review, the CMC reviewer, Dr. Hamid Shafiei states that “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.” The drug substance, glycerol phenylbutyrate (GPB) is a colorless to pale yellow liquid. It is manufactured and supplied by two different manufacturers. The drug product is (b) (4) drug substance filled into glass bottles and capped (b) (4). There are (b) (4).

4.2 Clinical Microbiology

Ravicti is not intended for intravenous use. No microbiology issues have been identified.

4.3 Preclinical Pharmacology/Toxicology

A 2-year carcinogenicity study in rats was positive, but the mechanism of tumor induction is not known. In the carcinogenicity study male and female Sprague-Dawley rats (65/sex/dose) were given doses of 0, 70, 210 and 650 mg/kg/day in males and 0, 100, 300, and 900 mg/kg/day in females. Neoplastic findings included an increased incidence of the following tumors:

- Pancreas: acinar cell adenoma, carcinoma and combined adenoma and carcinoma in both sexes
- Thyroid: follicular cell adenoma, carcinoma and combined adenoma and carcinoma in females
- Adrenal cortex: combined adenoma and carcinoma in females
- Uterus: polyp and combined polyp and sarcoma
- Zymbal's glands: carcinoma in both sexes
- Cervix

In order to assess the significance of these findings a scientific advisory panel was convened by the sponsor to review the proliferative changes reported to be due to HPN-100. The panel concluded that when evaluated using standard methods of assessment HPN-100 does not pose a carcinogenic risk for humans. Buphenyl was approved without carcinogenicity studies.

Genotoxicity studies were negative. HPN-100 was not genotoxic in the Ames bacterial reverse-mutation assay. The metabolites PAA, PAGN and PAG (Phenyl acetic glycine) were not genotoxic in the Ames test or in the in vitro chromosomal aberration test. PBA was not genotoxic in the Ames test, but was positive for the induction of structural chromosomal aberrations in the presence of metabolic activation, and negative in the absence of metabolic activation.

The metabolites formed from HPN-100 are not the same in humans and rats. Both humans and rats form PBA, but in non-primate species PAA conjugates with glycine instead of glutamine to form phenylacetyl glycine (PAG) instead of PAGN. Therefore in humans the pathway from HPN-100 to U-PAGN results in a lowering of glutamine. In rats the pathway from HPN-100 to PAG results in a depletion of glycine.

The Pharm/Tox reviewer Dr. Ke Zhang recommends the following wording be added to the Ravicti label:

In a 26-week study in transgenic (Tg.rasH2) mice, glycerol phenylbutyrate was not tumorigenic at doses up to 1000 mg/kg/day. In a two-year study in Sprague-Dawley rats, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma at 650 mg/kg/day in males (4.7 times the dose of 12.5 ml in adult patients, based on combined AUCs for PBA and PAA) and 900 mg/kg/day in females (8.4 times the dose of 12.5 ml in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at 900 mg/kg/day: 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. The dose of 650 mg/kg/day in male rats is 3 times the dose of 5.16 ml in pediatric patients, based on combined AUCs for PBA and PAA. The dose of 900 mg/kg/day in female rats is 5.5 times the dose of 5.16 ml in pediatric patients, based on combined AUCs for PBA and PAA.

Reviewer's Comment:

Reviewers from the Division of Pharmacovigilance were consulted regarding spontaneous report data and literature for human cases of malignancy reported as a complication of sodium phenylbutyrate use. The AERS database and the NIH PubMed did not identify any reports of malignancy as a possible adverse event.

The findings from the carcinogenicity studies should be included in the labeling for Ravicti. Since Buphenyl has the same active metabolite as Ravicti warnings in the Ravicti label concerning the carcinogenicity findings should also be required in the Buphenyl label.

4.4 Clinical Pharmacology

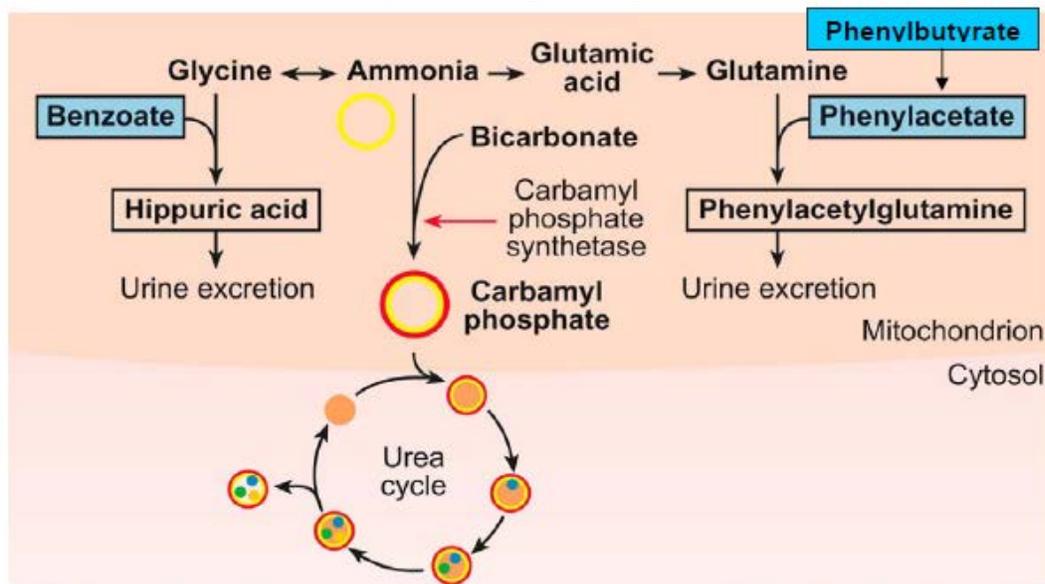
The bioavailability of HPN-100 compared to NaPBA was assessed in healthy subjects in Phase 1 study (UP1204-001). The pharmacokinetics of HPN-100 in UCD patients were assessed in four short-term controlled studies (UP1204-003, HPN-100-005, HPN-100-006, and HPN-100-012), in healthy adults in the thorough QTc study (HPN-100-010), and in cirrhotic patients (HPN-100-008 Part A&B).

4.4.1 Mechanism of Action

Ravicti belongs to the nitrogen scavenging class of drugs. Nitrogen scavenging drugs work through an alternative pathway to the Urea Cycle to provide for nitrogen disposal

in patients who are missing or severely deficient in one or more enzymes normally active in the Urea Cycle. Figure 5 shows ammonia disposal through the Urea Cycle, as well as the alternative route for nitrogen disposal followed by Ravicti (Phenylbutyrate).

Figure 5 Alternative Pathway for Nitrogen Disposal



[Ref: Summary Clinical Efficacy, Figure 2.7.3-9, p. 29 (modified from Summar, 2001b)]

HPN-100 is a triglyceride consisting of three molecules of PBA joined to glycerol in ester linkage. Pancreatic lipases cleave the ester bond to release PBA. Intact HPN-100 is not detectable in the systemic circulation of animals or humans. Next PBA is converted to PAA by beta oxidation; PAA is conjugated with glutamine in the liver and kidney via N-acylCoA-L-glutamine N-acyltransferase to form PAGN. PAGN is excreted in the urine, and contains two moles of waste nitrogen (like urea). At steady state dosing the proportion of PBA excreted in the urine as PAGN is very similar whether given as HPN-100 or NaPBA.

4.4.2 Pharmacodynamics

The main effect of Ravicti is to provide an alternate pathway for nitrogen excretion. Thus the main pharmacodynamic effect is to maintain serum ammonia at a desired level through the production of U-PAGN. The major PD marker, serum ammonia, is also the primary efficacy endpoint. The primary objective of the pivotal efficacy trial is to show that Ravicti is not inferior to Buphenyl in controlling ammonia levels. Pharmacokinetics and pharmacodynamics are inextricably related since the plasma level of the active moiety directly determines the level of ammonia.

A tQT study evaluating the effects of Ravicti at doses up to 19.8g per day (6mL TID) for 3 days on the QT/QTc interval showed that Ravicti had no QT/QTc prolonging effect. However the study was inconclusive because assay sensitivity was not demonstrated. Further discussion of this study is contained in section 7.4.5 of this review.

4.4.3 Pharmacokinetics

Full details concerning the Pharmacokinetics of Ravicti are contained in the Clinical Pharmacology review. Below is a brief summary of key PK findings.

Exposure:

In PK and safety study UP1204-003 the systemic exposure of PBA following HPN-100 administration was 27% lower than NaPBA (540 vs. 739 µg·h/mL). Exposure levels of PAA (575 vs. 596 µg·h/mL) and PAGN (1098 vs. 1133 µg·h/mL) were similar between the two drugs. HPN-100 showed less variability between peak and trough levels of PBA concentration compared to NaPBA. PAA concentrations, though were similar over a 24 hour period, peak levels were slightly higher for Buphenyl.

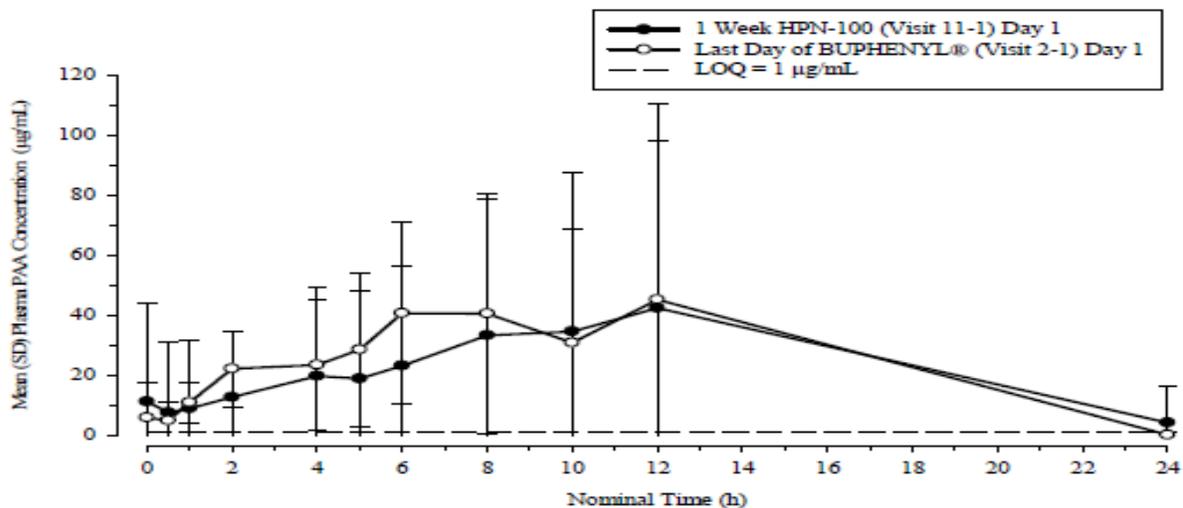
Table 2 PK Parameters (steady-state) NaPBA vs. HPN-100

PK Parameter	Arithmetic Mean (CV%)	
	NaPBA (N=10)	HPN-100 (N=10)
PBA in Plasma		
AUC (µg·h/mL)	739 (49)	540 (60)
C _{max} (µg/mL)	141 (44.5)	70.1 (64.7)
C _{min} (µg/mL)	0.588 (255)	2.87 (265)
PAA in Plasma		
AUC (µg·h/mL)	596 (124)	575 (169)
C _{max} (µg/mL)	53 (94.7)	40.5 (148)
C _{min} (µg/mL)	3.56 (194)	7.06 (311)
PAGN in Plasma		
AUC (µg·h/mL)	1133 (31)	1098 (44.2)
C _{max} (µg/mL)	83.3 (25.8)	71.9 (56)
C _{min} (µg/mL)	16.6 (86)	12.1 (134)

[Ref: UP1204-003, Table 18, p.67]

In Figure 6 shows that by hour twelve, both drugs behaved similarly with respect to PAA concentration.

Figure 6 Mean Plasma PAA Concentration-Time Profile



[Ref: UP1204-003, Figure 7, p.68.]

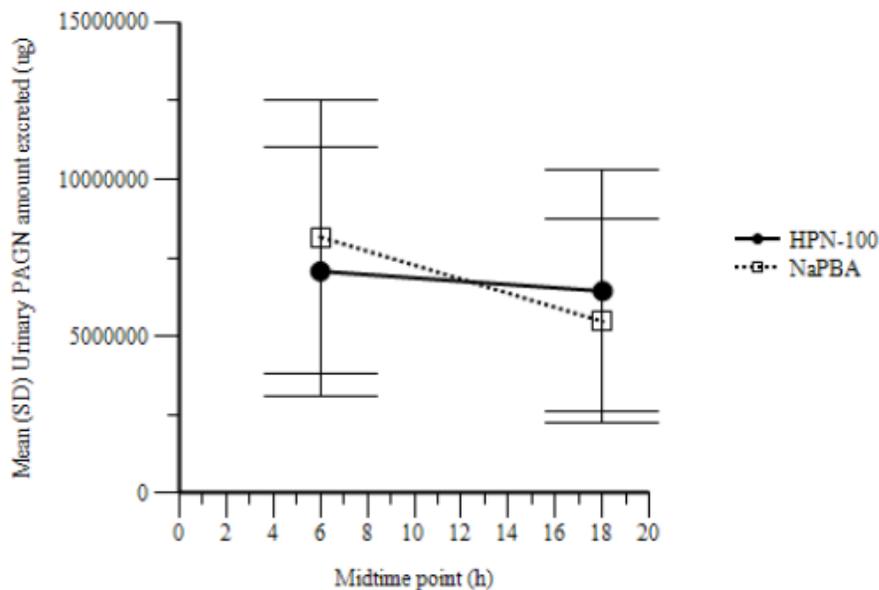
Half-Life:

Pancreatic lipases are the main enzymes responsible for hydrolysis of Ravicti and release of PBA. In vitro studies have shown that the half-life of the pre-prodrug Ravicti was <1 min and intact glycerol phenylbutyrate is not detected in the blood. In healthy volunteers receiving multiple doses of Ravicti, PAA and PAGN reached steady state in 2 to 3 days. As discussed in section 2, although pancreatic lipase is not active in the neonate, other forms of lipase are. Ravicti was not studied in neonates <29 days.

Excretion:

The final product of HPN-100 or NaPBA breakdown is PAGN. PAGN is excreted as urinary PAGN and in the process rids the body of waste nitrogen. During steady state dosing of UCD patients receiving an average of 12 mL/day of Ravicti, 24 hour U-PAGN averaged 13 g. The mean percentage of administered PBA excreted as PAGN was approximately 68.9 in adults and 66.4 in pediatric UCD patients. PAA and PBA represented minor urinary metabolites; each accounting for less than 1% of the administered dose of PBA. As Figure 7 shows, the total PAGN excretion over a 24 hour period is basically the same for both drugs, but the excretion of PAGN is more evenly distributed with HPN-100.

Figure 7 Mean U-PAGN excreted during Steady-State Dosing



Drug-drug interactions:

Since intact Ravicti is not detectable in the bloodstream, clinically important drug interactions are not likely. The reader is directed to the Clinical Pharmacology review for further discussion.

Hepatic Impairment:

In a study of patients with hepatic impairment receiving 6mL BID (13.2 g/day) Ravicti, PAA levels ranged from 14 to 358 $\mu\text{g/mL}$ with a mean PAA C_{max} of 144 $\mu\text{g/mL}$. At the higher dose of 9 mL BID PAA levels ranged from 57 to 655 $\mu\text{g/mL}$ with a mean C_{max} of 292 $\mu\text{g/mL}$. Patients with hepatic impairment appear to have a reduced rate of conversion of PAA to PAGN and these patients are at greater risk for PAA toxicity. In the label the sponsor proposes to reduce the recommended starting dose for patients with hepatic impairment.

Summary:

The major pharmacokinetic issues for Ravicti are dosing in pediatric patients below the age of 6, and PAA levels. Dosing in this age group is based on the PBA equivalent dose of Buphenyl. In a small study conducted by the sponsor in 15 pediatric patients the mean total daily dose of Ravicti was 4.68mL/day with a minimum dose of 0.80 mL/day and a maximum dose of 7.80 mL/day.

On day 10, steady state for Ravicti, the PK of the metabolites was measured. The highest PAA C_{max} was 480 $\mu\text{g/mL}$ in a patient receiving a total daily dose of Ravicti of 7.20 mL/day. The highest PAA C_{max} for a patient at steady state on Buphenyl was 530 $\mu\text{g/mL}$ at a Buphenyl dose of 3.10g/day. This same patient received a total daily dose

of Ravicti of 7.20 mL/day but did not have a PAA level for Ravicti because no blood sample was obtained.

Based on the data available for this review, there was no correlation between PAA levels and adverse events in UCD patients. For example the pediatric patient with the highest PAA on Ravicti (480 µg /mL) had an adverse event of vomiting. However the vomiting began while receiving NaPBA through a G-tube, increased on day 5 of the study, resolved on day 6, and was improved on day 10.

Reviewer's Comment:

Since conjugation of PAA with glutamine to form PAGN occurs in the liver, it is not surprising that patients with hepatic impairment have higher PAA levels.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 Tables of Clinical Trials

Study Number	Phase	Study Design	Study Objective	Subject Status/Patient Diagnosis	Number Exposed to HPN-100/Control(s) ^a
Subjects					
UP 1204-001	1	Randomized, open-label, cross-over	PK	Healthy	24/24/24/24 ^b
UP 1204-002	1	Uncontrolled	PK	Hepatic or healthy	32/-
HPN-100-008, Part A	1	Randomized, open-label, run-in	Hepatic impairment	Hepatic or healthy	15/-
HPN-100-010	1	Randomized, double-blind, crossover	Thorough QTc	Healthy	98/77/84 ^c
Patients					
UP 1204-003	2	Non-randomized, open-label, fixed-sequence, switch-over	Safety and efficacy	Adult UCD	10/14 ^d
HPN-100-005	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Pediatric UCD	11/11 ^d
HPN-100-006	3	Randomized, double-blind, crossover	Safety and efficacy	Adult UCD	44/45 ^d
HPN-100-005 safety-extension ^e	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Pediatric UCD	17/-
HPN-100-007 ^f	3	Uncontrolled	Safety	Adult and pediatric UCD	60/-
HPN-100-012	2	Non-randomized, open-label, crossover	Safety, PK	Pediatric UCD	15
HPN-100-012	2	Open-label, safety extension	Safety, ammonia control	Pediatric UCD	22

[Ref: Clinical Overview, Table 2.5-1, p. 8]

5.2 Review Strategy

The clinical review of efficacy for HPN-100 is done by one reviewer. Pivotal Phase 3 study HPN-100-006 will be discussed in detail in section 5.3. Phase 1 and 2 studies are discussed in section 6 Review of Efficacy, and section 7 Review of Safety when relevant. Only HPN-100-066 was powered for efficacy analysis. Pediatric study HPN-100-012SO will be discussed in section 5.2 because of its importance in providing data on pediatric patients.

5.3 Discussion of Individual Studies/Clinical Trials

In this section protocol HPN-100-006 will be discussed. The company and FDA reached agreement on a Special Protocol Assessment (SPA) for this trial, and there were no amendments.

HPN-010-006: A Phase 3, Randomized, Double-Blind, Cross-over, Active-Controlled Study of the Efficacy and Safety of HPN-100, Glyceryl tri-(4-phenylbutyrate), for the treatment of Adults with Urea Cycle Disorders.

Objective

The primary study objective is to establish the non-inferiority of HPN-100 to sodium phenylbutyrate (NaPBA) as assessed by venous ammonia.

Treatment Arms

Once study eligibility was confirmed subjects were randomly assigned in a blinded fashion and in a 1:1 ratio to receive treatment A or B.

Table 4 Treatment Arms

Arm	Period 1 (2 weeks)	Period 2 (2 weeks)
A	NaPBA + HPN-100 placebo	HPN-100 + NaPBA placebo
B	HPN-100 + NaPBA placebo	NaPBA + HPN-100 placebo

[Ref: Clinical Study Report HPN-100-006, Table 5, p.28]

Design

HPN-100-006 was a Phase 3, randomized, double-blind, active-controlled crossover study designed to assess the non-inferiority of HPN-100 to NaPBA by evaluating blood ammonia levels in adult patients with UCDs. Subjects were admitted to the clinical research unit for 24 hours of PK blood and urine sampling at the end of each treatment period, which is the steady state for each drug. Patients are required to follow a stable diet and record protein intake.

Population

The population studied was adult patients ≥ 18 years of age with a confirmed diagnosis of UCD involving deficiencies of CPS, OTC, or ASS, who were being treated with NaPBA (and on a stable dose) and had controlled ammonia levels ($<100 \mu\text{mol/L}$ without signs and symptoms of hyperammonemia).

Assessments

Patients were monitored by laboratory tests, amino acid panel, vital signs, and ECG monitoring. PK blood and urine and venous ammonia levels were also obtained on a fixed schedule. Table 5 shows the schedule of assessments:

Table 5 HPN-100-006 Schedule of Study Assessments

Window (+/-days)	Screen	Day 1	Day 7	Day 14	Day 15	Day 21	Day 28	Day 29
Visit No.	1	2	3	4	NA	5	6	NA
Informed Consent	X							
Inclusion / Exclusion	X							
Medical History	X							
Physical Exam (including neurological assessment)	X		X	X		X	X	
Concomitant Medications	X	X		X			X	
Weight	X			X			X	
Height	X							
Vital Signs	X	X	X	X		X	X	
Safety Labs	X	X	X	X		X	X	
ECG	X	X	X	X		X	X	
Urine Pregnancy Test	X	X	X	X			X	
Single Blood Sample for Ammonia	X	X	X			X		
Single Blood Sample for PK		X	X			X		
Spot Urine				X	X		X	X
Randomize		X						
Calculate NaPBA/HPN-100 Dose	X							
Dispense Period 1 Study Drug 1 with compliance diary		X						
Start Initial Treatment		X						
Collect Compliance Diary and Assess study drug compliance				X			X	
Dispense Study Drug Period 2 with compliance diary					X			
Start Second Treatment					X			
Collect Study Drug Bottles					X			X
Dispense Diet Diary and perform Diet Assessment and Counseling		X		X			X	
Collect Diet Diary				X			X	
SF-36		X						
Offer HPN-100-007 Study								X
Adverse Events		X	X	X	X	X	X	X
24-hr Ammonia Samples				X			X	
24-hour Urine Sampling		X	X	X		X	X	
Amino Acid Panel		X		X			X	
24-hr PK Blood Samples				X			X	
Discharge					X			X

Best Available Copy

[Ref: HPN-100-006, Appendix A, p.60]

Primary Endpoint

The primary endpoint was the 24-hour area under the curve (AUC₀₋₂₄) for blood ammonia on days 14 and 28. These days marked the end of both drug treatment periods.

Secondary Endpoints

Secondary Endpoints Included:

- Maximum blood ammonia values observed on NaPBA versus HPN-100
- Rate (%) of blood ammonia values above the upper limit of normal on NaPBA versus HPN-100
- Number and severity of symptomatic hyperammonemic crises
- Correlation between 24-h urinary PAGN excretion (U-PAGN₀₋₂₄) and blood ammonia AUC₀₋₂₄)

PK parameters included AUC₀₋₂₄ and C_{max} for major metabolites of NaPBA and HPN-100 including plasma PAA, PBA, PAGN, and U-PAGN.

Statistical Considerations

A sample size of 44 evaluable subjects was selected to provide 90% power to demonstrate that the ratio of the means of NH₃ 24-hour AUC between HPN-100 and NaPBA does not exceed 1.25.

DSMB

An independent DSMB will review the safety data when approximately 50% of subjects have been enrolled, and they will be notified and convened if any study stopping rules are met.

Inclusion Criteria

- Diagnosis of UCD involving deficiencies of CPS, OTC, or ASS, confirmed via enzymatic, biochemical, or genetic testing
- Age 18 years or older; on a stable dose of NaPBA for at least one week before day 1 visit. If not previously on treatment, could be started on NaPBA during screening period and enrolled in study as long as on stable dose NaPBA for at least 1 week before day 1
- No clinical evidence hyperammonemia associated with an ammonia level of ≥ 100 $\mu\text{mol/L}$ during 2 weeks preceding screening
- Signed informed consent
- Able to perform study activities and blood draws and 24-hour urine sample
- Negative pregnancy test for females of childbearing potential
- On acceptable method of contraception

Exclusion Criteria

- Screening or baseline ammonia ≥ 100 $\mu\text{mol/L}$ or signs and symptoms of hyperammonemia during 2 week period preceding screening
- Use of any investigational drug within 30 days of Day 1
- Active infection or intercurrent condition that may have increased ammonia levels
- Clinical or laboratory abnormality of Grade 3 or greater severity according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0, except Grade 3 elevation in liver enzymes defined as levels 5-20 times ULN in ALT, AST, or GGT in a clinically stable subject
- Clinical or laboratory abnormality or medical condition that may put the patient at increased risk
- Any medication known to affect renal clearance or increase protein catabolism within 24 hours prior to Day 1 and throughout the study
- Use of sodium benzoate within one week of Day 1
- History of QTc interval prolongation or QTc interval >450 msec at screening or baseline
- Known hypersensitivity to PAA or PBA
- Liver transplant, including hepatocellular transplant
- Breastfeeding or lactating female

Investigational Product

HPN-100 and NaPBA will be given orally three times daily with meals. The identical (PBA mole equivalent) daily dose of HPN-100 to match the NaPBA daily dose will be administered to ensure consistent metabolic control. No adjustment to the NaPBA or HPN-100 dose or schedule is allowed during the study. The 100% HPN-100 dose-equivalent to 100% NaPBA dose is calculated from the following formula.

$$\text{NaPBA dose (g)} \times 0.95/1.1 = \text{Total daily HPN-100 dose (mL)}$$

The maximum total daily dose of HPN-100 allowed in the study is 17.4 mL/day, which corresponds to 20 grams NaPBA.

Duration of Study

The screening period is within 30 days of Day 1. Subjects can be put on a stable dose of NaPBA during this period. The treatment period is days 1 to 28, which allows 2 weeks dosing for each drug/placebo.

Stopping Rules

Subjects meeting any of the following had to be withdrawn from the study:

- hyperammonemic crisis (clinical symptoms associated with ammonia levels equal or over 100 $\mu\text{mol/L}$)
- AE of Grade 4 or greater using CTCAE terminology, or life-threatening AE if not covered by CTCAE
- clinically significant allergy or hypersensitivity reactions to HPN-100
- QTc>500 msec or increase from baseline of >60 msec
- liver transplant
- pregnancy

Stopping Rule for Study

- 2 subjects with Grade 4 or greater AE of same preferred term, excluding hyperammonemia and conditions present at baseline; enrollment will be paused pending DSMB determination as to whether enrollment should resume
- if hyperammonemic events occur in 25% of 10 enrolled subjects, or 4 subjects, whichever is lower, enrollment will be paused pending DSMB determination

Reviewer's Comment:

The protocol was submitted as a SPA. Several key areas are worth discussing. One was regarding the exclusion of pediatric patients in this pivotal phase 3 study. The FDA did not allow pediatric patients to be enrolled because of a lack of pharmacokinetic data in the pediatric population. The sponsor was told they needed to conduct a separate PK and safety study in pediatric patients in order to inform dosing. Another consideration was use of a placebo arm. Use of a placebo arm was not possible due to the untenable consequences of hyperammonemia. Without use of a nitrogen scavenging drug UCD patients are at high risk for hyperammonemia. Therefore a placebo arm was considered

unethical. Because the two drugs are essentially the same, effects of period 1 were not likely to affect period 2. Only three UCD subtypes were enrolled in this trial because these are the only three UCD subtypes for which the active comparator Buphenyl is approved. Finally, the dose of Ravicti was based on the dose of Buphenyl. The dose of NaPBA was based on the severity of enzyme deficiency, diet and intake of amino acids or supplements. The specifics of dose selection were not provided.

HPN-100-012:

Next is a discussion of pediatric study HPN-100-012, **A Switch-Over, Open-Label Study of the Safety, Pharmacokinetics, and Efficacy of HPN-100, Followed by Long-Term Treatment with HPN-100 in Pediatric Subjects less than 6 years of age with Urea Cycle Disorders (UCDs).**

Objective

The objectives of this study are to assess safety, pharmacokinetics, and ammonia control in pediatric UCD patients 29 days to <6 years of age during treatment with HPN-100.

Treatment

On day 1 patients are observed in an inpatient setting for at least 24 hours while receiving NaPBA. On or after day 2 patients still eligible for the study are switched to HPN-100 and remain inpatients until the investigator deems them clinically controlled. HPN-100 is to be administered prior to breastfeeding by the mother or administration of formula or food. TID or QID feeding and administration of drug is recommended but previously established NaPBA dosing regimen can be followed based on patient's feeding habits. Subjects will receive HPN-100 at a dose that delivers the same amount of PBA as NaPBA. Each gram of NaPBA delivers 0.88g of PBA and each milliliter (mL) of HPN-100 delivers 1.02g.

Design

The study is an open-label study consisting of a 10-day switch-over period, followed by a long-term treatment period with HPN-100 for up to 12 months (HPN-100-012SE).

Population

In the protocol the sponsor explained that the patient population excluded newborns (0-28 days old) since UCD patients presenting clinically in the first month of life usually have the most severe defects in urea synthesis, and typically present in crisis. In addition the newborn digestive system is immature with respect to fat digestion (although aided by the presence of lipases in human breast milk). The study population included infants/toddlers, and children up to age 6.

Assessments

Table 6 shows the schedule for the cross-over study and the safety extension. Day 1 through 10 represent the cross-over period, and show that single samples of ammonia

are obtained on day 2, 3, and 24-hour ammonia and PK are obtained on day 1 and day 10.

Table 6 HPN-100-012 Schedule of Assessments

	NaPBA		Transition		HPN-100		Long-Term Treatment			Month 12
	Screen ¹	Day 1	Day 2	Day 3 ²	Day 10	Month 0	Week 1 ³	Month 1, 2 ²	Month 3, 6, 9	Early Term ⁴
Window (+/- days)	30	NA	NA	NA	4	NA	3	7	14	
Admit		X			X					
Discharge			X	X		X				
Informed Consent	X									
Inclusion / Exclusion	X									
Medical History	X									
Physical and Neurological Exam	X	X			X		X	X	X	X
Concomitant Medications	X	X	X		X		X	X	X	X
Data Points of Interest	X	X			X				X	X
Height	X				X				X	X
Weight	X	X			X			X	X	X
Vital Signs ⁵	X	X	X	X	X		X	X	X	X
Safety Labs	X	X			X			X ⁶	X	X
24-hour Ammonia and PK		X			X					
24-hour Urine ⁷		X			X			X ⁸	X ⁸	X ⁸
Single Sample for Ammonia ⁸	X		X	X			X	X	X	X
Single Plasma PK ⁹								X	X ⁹	X
Amino Acid Panel		X			X			X	X	X
Record Prescribed Dietary Protein and Calories ¹⁰	X						X	X	X	X
Record Protein and Calorie Intake ¹¹		X			X					
Study Drug Preference Questionnaire		X				X				X
Adverse Events		X	X		X		X	X	X	X
Neuropsychological Battery ¹²		X								X
Study Drugs										
NaPBA Treatment	X	X								
Dispense HPN-100		X				X ¹³			X	
Start Transition to HPN-100			X							
HPN-100 Treatment				X	X	X	X	X	X	X
Begin Long-Term Treatment						X				

[Ref: HPN-100-012 Clinical Study Report, Table 3, p.25.]

Primary Endpoint

There is not an efficacy endpoint per se since the study is designed to assess safety, PK and ammonia control, but not powered for efficacy assessment. Outcomes of interest included rate of AEs, AUC₀₋₂₄ of blood ammonia on days 1 and 10, mean and maximum blood ammonia levels days 1 and 10, plasma PBA, PAA, and PAGN on NaPBA vs. HPN-100, and urinary excretion PAGN day1 and 10.

For the long-term treatment phase assessments included rate of AEs, mean and maximum blood ammonia levels on HPN-100 compared with pre-enrollment data on NaPBA, frequency of hyperammonemic crises on HPN-100 compared with pre-enrollment period, and frequency of ammonia levels > 2 times upper limit of normal on HPN-100 compared with pre-enrollment NaPBA.

Statistical

No statistical analysis was planned.

DSMB

An independent DSMB will be chartered to oversee the safety of the study subjects. The DSMB will review safety data and be notified if sponsor is made aware of a serious adverse event, or if a subject meets any stopping rules.

Inclusion Criteria

- Aged 29 days to <6 years
- Informed consent from legally acceptable representative
- Suspected or confirmed UCD diagnosis of any subtype except NAGS
- On stable dose NAPBA powder for at least 5 days before day 1
- Not receiving NaBz for at least 5 days before day 1
- No concomitant illness which would preclude safe participation
- Able to receive medication orally
- Has not undergone liver or hepatocellular transplantation
- Judged sufficiently stable and compliant with diet and treatment to be suitable for enrollment

Exclusion Criteria

- Screening ammonia ≥ 100 $\mu\text{mol/L}$ and signs and symptoms of hyperammonemia
- Use of any investigational drug within 30 days of Day 1
- Active infection or intercurrent condition that may have increased ammonia levels
- Clinical or laboratory abnormality of Grade 3 or greater severity according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0, except Grade 3 elevation in liver enzymes defined as levels 5-20 times ULN in ALT, AST, or GGT in a clinically stable subject
- Clinical or laboratory abnormality or medical condition that may put the patient at increased risk
- Known hypersensitivity to PAA or PBA
- Liver transplant, including hepatocellular transplant
- Currently treated with Carbaglu

Stopping Rules for Individual Patients

- Clinically significant allergy or hypersensitivity reactions to HPN-100
- Hyperammonemic crisis while receiving HPN-100
- Liver or hepatocellular transplant

Withdrawal of Patients Due to Hyperammonemic Crisis

- If a patient experiences a HA crisis while on NaPBA (day 1) NaPBA may be stopped and restarted after patient becomes stable. Patient could continue in transition to HPN-100 at discretion of investigator.

- If patient had HA crisis during switch-over, after transitioning to HPN-100 patient will be withdrawn from switch-over, but was eligible for long term enrollment when clinically stable

Reviewer's Comment:

Neonates less than 29 days were not included in this study because they are considered too ill and often require intensive care support. Dosing is based on a patient's previous dose of sodium phenylbutyrate and no dose titration was permitted in this cross-over study.

6 Review of Efficacy

6.1 Indication

The indication being sought is adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders (UCD) involving deficiencies of the following enzymes or transporters: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (ARG), and mitochondrial transporter ornithine translocase (HHH).

6.1.1 Methods

No pooling of clinical efficacy data was done since only one Phase 3 efficacy study was conducted. An outline of the trial design of the pivotal Phase 3 trial, and the pediatric clinical trial HPN-100-012 is contained in section 5.3.

6.1.2 Demographics

Demographics are described for 80 patients in short-term controlled studies and 100 patients in open-label safety extension studies. Female patients outnumber males almost 2 to 1. In short-term studies most patients were around 25 years of age (range 0.2 to 75). In long-term studies the mean age dropped to 19 (range 0.2 to 60). The most common UCD diagnosis was ornithine transcarbamylase deficiency (OTC), which is the most common of the urea cycle disorders.

Table 7 shows demographic characteristics of UCD patients.

Table 7 Baseline Characteristics UCD Population Receiving Ravicti

Demographics		Short-term studies (n=80)	Long-term studies (n=100)
Total enrolled	Study 003	10	NA
	Study 006	44	NA
	Study 005	11	17
	Study 007	NA	60
	Study 012	15	23
Gender	Male	26 (32.5)	33 (33)
	Female	54 (67.5)	67 (67)
Age	Mean (SD)	24.49 (17.62)	19.64 (15.86)
	Range	0.2-75.0	0.2-60.0
Age at Initiation of Ravicti [n (%)]	29 days to <2 yrs.	4 (5)	7 (7)
	2-5 yrs.	11 (14)	16 (16)
	6-11 yrs.	7 (9)	17 (22)
	12-17 yrs.	4 (5)	9 (12)
	≥ 18 yrs.	54 (68)	51 (66)
UCD Diagnosis [n (%)]	OTC Deficiency	60 (75)	69 (69)
	CPS 1 Deficiency	1 (1)	1 (1)
	ASS Deficiency	8 (10)	12 (12)
	ARG Deficiency	1 (1)	2 (2)
	ASL Deficiency	9 (11.3)	13 (13)
	HHH Syndrome	1 (1)	3 (3)

[Ref: Adapted from 120-day summary report, Table 4, p.29.]

Table 8 shows that all but one patient (for whom data are missing) had been taking NaPBA prior to enrollment in the trial. The table also shows that in pivotal study 006 twenty percent of patients had one or more hyperammonemic crisis in the preceding year before enrollment. In the smaller phase 2 study UP1204-003 the number is as high as 43%.

Table 8 Additional Baseline Characteristics

Characteristic	Short-Term Controlled Studies			Long-Term Open-Label Studies	
	UP 1204-003 (N = 14)	HPN-100-005 (N = 11)	HPN-100-006 (N = 45)	HPN-100-005 SE (N = 26)	HPN-100-007 (N = 60)
Duration of NaPBA Treatment	Months	Months	Months	Months	Months
n	14	11	44	17	53
Mean (SD)	97.89 (88.406)	74.68 (48.22)	128.57 (97.414)	62.50 (45.744)	126.79 (96.954)
Median	7.00	76.0	120.00	68.00	120.00
Range	0.0, 25.0	0.5, 162	0.2, 300.0	0.5, 162.0	0.2, 300.0
Form of NaPBA Treatment [n (%)]					
Powder	4 (28.6) ^c	7 (63.6) ^c	8 (17.8) ^c	11 (64.7)	14 (23.3)
Tablet	10 (71.4)	4 (36.4)	36 (80.0)	6 (35.3)	39 (65.0)
Missing	–	–	1 (2.2)	–	7 (11.7)
Daily Dose of NaPBA Treatment	g/day	g/day	g/day	g/day	g/day
n	14	11	45	17	53
Mean (SD)	13.49 (6.075)	12.41 (4.392)	14.54 (6.808)	11.32 (4.576)	14.08 (6.513)
Median	12.78	10.50	15.00	10.50	13.50
Range	0.5, 24.0	8.0, 20.0	1.5, 36.0	2.3, 20.0	1.5, 36.0
Number of Hyperammonemic Crises During 12 Months Before Enrollment	8	7	18	8	16
Number of Patients with ≥ 1 Hyperammonemic Crisis within 12 Months Before Enrollment [n (%)]	6 (42.9)	4 (36.4)	9 (20.0)	5 (29)	10 (17)

[Ref: ISE Table 2.7.3-22 p.79]

Reviewer’s Comment:

Hyperammonemic crises are not uncommon in patients on pharmacologic therapy for UCDs. Events precipitating hyperammonemia are events in which the nitrogen load is increased, and include non-compliance with medication, non-compliance with dietary restrictions, and intercurrent illnesses.

6.1.3 Subject Disposition

The disposition of patients enrolled in short-term and long-term studies is shown in Table 9. No patients receiving Ravicti in short-term studies withdrew; five patients receiving the active comparator Buphenyl withdrew. Two of the five Buphenyl withdrawals were for the adverse event of hyperammonemia.

Table 9 Patient Disposition, Pooled Analysis

Characteristic [n (%)]	Short-Term Controlled Studies (ITT Population) ^a		Long-Term Open-Label Studies (Safety Population) ^b
	NaPBA (N = 70)	HPN-100 (N = 65)	HPN-100 (N = 77)
Total Patients^c	70 (100.0)	65 (100.0)	–
UP 1204-003d	14	10 ^e	–
HPN-100-005	11	11	–
HPN-100-006	45	44 ^f	–
HPN-100-005 SE	–	–	17
HPN-100-007	–	–	60
Patients Who Completed Study	65 (92.9)	65 (100.0)	69 (89.6)
Patients Who Withdrew from Study	5 (7.1)	0	8 (10.4)
Reasons for Withdrawal from Study^g			
Adverse event	2 (2.9)	0	1 (1.3)
Protocol violation	0	0	0
Lost to follow-up	0	0	0
Withdrew consent	2 (2.9)	0	6 (7.8)
Investigator request	1 (1.4)	0	0
Other	0	0	1 (1.3)

[Ref: ISE Table 2.7.3-19, p.75]

Fifteen patients were enrolled in pediatric switch-over study HPN-100-012, including 4 patients aged 29 days to <2 years, and 11 patients aged 2 to <6 years. All patients completed the cross-over study and none have discontinued from the ongoing safety extension.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for the Phase 3 trial 006 was blood ammonia AUC₀₋₂₄ on Days 14 and 28 in adult patients with UCs. Ammonia is a surrogate for morbidity and mortality in UCD patients, and high ammonia levels are associated with adverse neurological outcomes, including coma and death. Data from a large open-label clinical study using an intravenous infusion of sodium phenylacetic acid and sodium benzoate in patients with UCs support the relationship between elevated ammonia levels and these outcomes⁴. Further, the agency has previously accepted plasma ammonia level as a primary endpoint in clinical trials for products approved for the treatment of UCs. For example, in the marketing application for carglumic acid for the treatment of N-Acetylglutamate Synthetase (NAGS) deficiency the primary efficacy evaluation was based on treatment effect on short-term ammonia levels, and for the approval of Buphenyl ammonia control with drug and diet was the primary measure of efficacy.

In Study 006 the non-inferiority of Ravicti to Buphenyl was assessed by evaluating blood ammonia in 44 adult patients who were being treated with Buphenyl to control their disease. Patients were randomized to either Buphenyl /Ravicti placebo, or Ravicti/Buphenyl placebo, and treated for two weeks on each. The dose of Ravicti was

4 Enns, Gregory et al. Survival after Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders. NEngJMed 2007; 356:p.9.

calculated to provide the same amount of PBA as Buphenyl. Patients underwent 24 hours of ammonia measurements after two weeks of dosing. The results of the 4 week trial show that Ravicti is non-inferior to Buphenyl based upon meeting the pre-specified non-inferiority margin of 1.25 (upper bound of 95% confidence interval).

Table 10 Non-Inferiority Analysis Study 006

Blood Ammonia ₀₋₂₄ Statistic (µmol·h/L) ^a	NaPBA	HPN-100	Difference Between HPN-100 and NaPBA
ITT	n=44	n=44	n=44
Mean	976.63	865.85	-111
SD	865.352	660.529	579.0
Median	652.48	672.59	-47
Min, Max	301.9, 4665.9	206.0, 3351.1	-2953, 1007
Ratio of Geometric Means ^b			0.91
90% Confidence Interval ^b			(0.816, 1.012)
95% Confidence Interval ^b			(0.799, 1.034)
MITT	n=43	n=43	n=43
Mean	985.61	867.67	-118
SD	873.517	668.234	583.8
Median	674.18	655.52	-74
Min, Max	301.9, 4665.9	206.0, 3351.1	-2953, 1007
Ratio of Geometric Means ^b			0.90
90% Confidence Interval ^b			(0.807, 1.002)
95% Confidence Interval ^b			(0.789, 1.024)
PP	n=43	n=43	n=43
Mean	985.47	868.29	-117.18
SD	873.578	668.145	584.224
Median	674.18	655.52	-74.32
Min, Max	301.9, 4665.9	206.0, 3351.1	-2952.9, 1006.6
Ratio of Geometric Means ^b			0.90
90% Confidence Interval ^b			(0.809, 1.007)
95% Confidence Interval ^b			(0.792, 1.030)

[Ref: Clinical Study Report – HPN-100-006, Table 15, p.64]

Reviewer's comment:

Choice of active control and non-inferiority design are appropriate for evaluating the effectiveness of Ravicti. Buphenyl is approved for treatment of UCDs and has been used since 1996. Both drugs are transformed into the same active moiety, and the main difference between the two relates to formulation and palatability.

All ammonia values were converted to the SI unit (µmol/L) before normalization, imputation and calculation of the AUC. Data were obtained from different laboratories, using slightly different normal reference ranges. Therefore the ammonia data had to be normalized to a standard laboratory reference range before conducting the primary efficacy analyses. The formula that was applied was $s=x*(U_s/U_x)$. S is the normalized laboratory value, x is the original laboratory value, U_x is the upper limit of the normal reference range from the original laboratory, and U_s is the upper limit of the normal reference range for the standard laboratory. For example, if a value of 10 was obtained

from a local laboratory with a normal range of 5 – 25, and it is normalized to a standard reference range that was established to be 10 – 35, then by applying the above formula, the normalized value would be 14 ($s = 10 * (35 / 25) = 14$).⁵

Reviewer’s Comment:

The normalization scheme for ammonia appears reasonable, and was outlined in the Statistical Analysis Plan reviewed by the FDA.

Other studies submitted with this application were open-label, fixed-sequence, and switch over-studies to compare control of blood ammonia on Ravicti to control of blood ammonia on sodium phenylbutyrate. Persistence of ammonia control was also monitored in long-term safety extension studies.

Table 11 Non-Inferiority Analysis of Blood Ammonia AUC0-24 across Studies

Statistic	Across Studies:								Pooled Primary Efficacy Analysis:			
	UP 1204-003 (N = 14)		HPN-100-005 (N = 11)		HPN-100-006 (N = 45)		HPN-100-012 (N = 15)		Original NDA (N = 70)		Updated Analysis (N = 85)	
	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100
N	12	10	11	11	44	44	15	13	67	65	82	78
Mean	1303.48	724.02	813.48	602.17	976.63	865.85	914.43	647.63	1008.38	799.41	991.19	774.11
SD	1082.250	314.950	322.109	188.087	865.352	660.529	630.206	379.944	849.497	568.528	811.164	542.579
Median	1120.67	676.43	886.74	538.90	652.48	672.59	604.96	543.08	738.08	622.17	736.53	593.00
Min	384.7	195.9	279.7	446.4	301.9	206.0	189.3	258.6	279.7	195.9	189.3	195.9
Max	4341.3	1164.1	1279.2	1063.6	4665.9	3351.1	1974.8	1513.5	4665.9	3351.1	4665.9	3351.1
Difference Between HPN-100 and NaPBA	UP 1204-003 (N = 14)		HPN-100-005 (N = 11)		HPN-100-006 (N = 45)		HPN-100-012 (N = 15)		Original NDA (N = 70)		Updated Analysis (N = 85)	
Mean difference	-367.55		-211.31		-110.78		-237.46		-167.29		-178.99	
SD	576.952		309.643		578.951		439.445		543.865		525.964	
Median difference	-88.05		-133.41		-46.70		-37.84		-86.60		-70.88	
Min, max difference	-1743.8, 147.2		-816.1, 215.4		-2952.9, 1006.6		-1484.8, 99.6		-2952.9, 1006.6		-2952.9, 1006.6	
Ratio of geometric means ^a	0.63		0.78		0.91		0.79		0.84		0.84	
p-value ^b	0.075		0.047		0.211		0.075		0.016		0.004	
p-value ^c	0.084		0.054		0.315		0.033		0.013		0.002	
90% CI ^d	(0.398, 1.012)		(0.589, 1.032)		(0.816, 1.012)		(0.625, 1.002)		(0.755, 0.941)		(0.755, 0.929)	
95% CI ^e	(0.361, 1.116)		(0.556, 1.095)		(0.799, 1.034)		(0.593, 1.055)		(0.739, 0.962)		(0.740, 0.949)	

[Ref: ISS-120 day safety update, Table 4.2.1, p.30.]

Reviewer’s Comment:

Although each study listed in Table 11 falls within the non-inferiority margin, they were not powered for efficacy.

6.1.5 Analysis of Secondary Endpoints(s)

Among the secondary endpoints analyzed in Ravicti studies were:

- Maximum blood ammonia levels with HPN-100 and NaPBA
- Rate (percentage) of ammonia values above upper limit of normal (ULN) on NaPBA versus HPN-100
- Number and severity of symptomatic hyperammonemic crises

5 Integrated Summary of Safety. Statistical Analysis Plan. Section 5.4.1, p.16.

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- Correlation between U-PAGN₀₋₂₄ excretion and blood ammonia AUC₀₋₂₄

Maximum blood ammonia levels. Mean ammonia C_{max} values were lower with HPN-100 compared to NaPBA across patient populations. Mean blood ammonia AUC₀₋₂₄ was also lower with HPN-100 compared to NaPBA.

Table 12 Mean Blood Ammonia AUC₀₋₂₄ and C_{max}

	Ammonia AUC ₀₋₂₄ (μmol·h/L) ^a			Ammonia C _{max} (μmol/L)		
	NaPBA	HPN-100	Difference between HPN-100 and NaPBA	NaPBA	HPN-100	Difference between HPN-100 and NaPBA
ITT	n=44	n=44	n=44	n=44	n=44	n=44
Mean	976.63	865.85	-110.78	70.83	60.94	-9.89
SD	865.352	660.529	578.951	66.705	46.213	43.088
Median	652.48	672.59	-46.70	45.95	50.70	-3.58
Min	301.9	206.0	-2952.9	13.5	12.1	-163.3
Max	4665.9	3351.1	1006.6	303.3	245.0	85.0

[Ref: HPN-100-006 CSR, Table 16, p.65]

Elevated Ammonia Values. The ULN for blood ammonia, after normalization, was 35 $\mu\text{mol/L}$. The data below for the ITT population show that the number of samples above the ULN is highly dependent upon the time frame analyzed. For example at 2 hours post dose 46.5% of HPN-100 samples were above ULN compared to 31% for NaPBA. Conversely, at 16-h post-dose 40.5% of NaPBA samples were above ULN compared to 26.8% Ravicti. When all time points are combined, the values are almost identical.

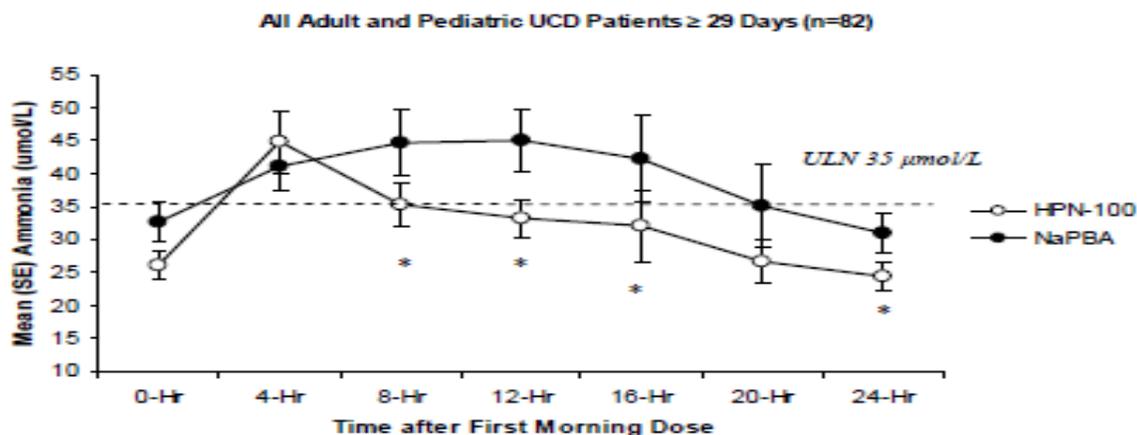
Table 13 Ammonia Values above Upper Limit Normal

Number of Samples with Ammonia Values above the ULN ^{a,b}	NaPBA		HPN-100	
	n	Number of Samples > ULN, n (%)	n	Number of Samples > ULN, n (%)
ITT				
Pre-dose	44	15 (34.1)	44	13 (29.5)
2-h post dose	42	13 (31.0)	43	20 (46.5)
4-h post dose	44	20 (45.5)	43	22 (51.2)
8-h post dose	42	18 (42.9)	43	17 (39.5)
12-h post dose	43	13 (30.2)	42	15 (35.7)
16-h post dose	42	17 (40.5)	41	11 (26.8)
20-h post dose	44	14 (31.8)	44	12 (27.3)
24-h post dose	44	15 (34.1)	43	12 (27.9)
All time points	345	125 (36.2)	343	122 (35.6)

[HPN-100-006, Table 18, p.69]

In a pooled analysis of pediatric and adult UCD patients over a 24 hour period only one reading for HPN-100 was above the ULN (4-HR), whereas at four time-points the mean ammonia level for NaPBA was above the ULN.

Table 14 Pooled Analysis: Mean Blood Ammonia



[Ref: ISS-120 day, Figure 9, p.34]

Hyperammonemic crisis (HAC) is defined in the UCD protocols as blood ammonia greater than 100µmol/L plus signs and symptoms of hyperammonemia (headache, nausea, depressed consciousness ranging from lethargy to coma). Although change in diet or intercurrent illness can be the cause of HA crisis, sometimes the cause is not known.

In short-term controlled studies no patient taking HPN-100 had a HA crisis, while two patients taking NaPBA had a HA crisis. In long-term open-label studies without active control (Table 15) the number of hyperammonemic crisis is less for pediatric and adult patients than in the preceding twelve months. No hyperammonemic crisis occurred during the switch over part of study HPN-100-012.

Table 15 Hyperammonemic Crisis Long-Term Studies HPN-100

	Pediatrics 6-17 years (n=26)	Adults ≥ 18 years (n=51)	Total (n=77)
History Hyperammonemic Crisis			
Number of patients (n, %)	6 (23.1)	9 (17.6)	15 (19.5)
Number of events	9	15	24
Hyperammonemic crisis on study treatment			
Number of patients	5 (19.2)	7 (13.7)	12 (15.6)
Number of events	5	10	15

[Ref: Adapted from Summary clinical Safety, Table 2.7.4-34, p. 83.]

Correlation Blood Ammonia with HPN-100 or NaPBA metabolites

Analysis of the correlation between blood ammonia AUC₀₋₂₄ and U-PAGN₀₋₂₄ are shown below. There was a correlation between drug dose and metabolites with the strongest correlation between HPN-100 and NaPBA and U-PAGN (r=0.795 for HPN-100 and r=0.800 for HPN-100).

Table 16 Correlation Total Dose with Blood Ammonia and Metabolites

Metabolite	Variable	HPN-100		NaPBA		Overall	
		Coefficient (r) ^a	p-value ^a	Coefficient (r) ^a	p-value ^a	Coefficient (r) ^a	p-value ^a
Fasting Ammonia	24 h (µmol/L)	0.048	0.762	0.323	0.033	0.190	0.077
U-PAGN ^b	0-24 h excretion (µg)	0.795	< 0.001	0.800	< 0.001	0.791	< 0.001
	0-12 h excretion (µg)	0.683	< 0.001	0.731	< 0.001	0.685	< 0.001
	12-24 h excretion (µg)	0.738	< 0.001	0.780	< 0.001	0.747	< 0.001
Plasma PAGN	AUC ₀₋₂₄ (µg·h/mL)	0.760	< 0.001	0.738	< 0.001	0.736	< 0.001
	24 h (µg/mL)	0.815	< 0.001	0.649	< 0.001	0.699	< 0.001
Plasma PAA	AUC ₀₋₂₄ (µg·h/mL)	0.648	< 0.001	0.732	< 0.001	0.661	< 0.001
	24 h (µg/mL)	0.556	< 0.001	0.219	0.153	0.406	< 0.001
Plasma PBA	AUC ₀₋₂₄ (µg·h/mL)	0.597	< 0.001	0.708	< 0.001	0.641	< 0.001
	24 h (µg/mL)	0.688	< 0.001	0.128	0.409	0.439	< 0.001

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[Ref: HPN-100-006, Table 24, p.79]

b-correlation obtained using Spearman rank-order correlation

Reviewer's Comment:

Among the variables discussed above U-PAGN is particularly important since it correlates with nitrogen disposal and ammonia levels. The amount excreted by both Ravicti and Buphenyl is very similar, further confirming that the performance of both drugs is comparable.

6.1.6 Other Endpoints

Plasma PBA, PAA, and PAGN levels. The PK parameters from HPN-100-006 included plasma PBA, PAA, and PAGN levels. At steady state the exposure and maximum concentration of each metabolite is lower with HPN-100 than NaPBA.

Table 17 PK parameters at Steady State – HPN-100 vs. NaPBA (ITT)

Plasma PK Parameters	Arithmetic Mean (CV %)	
	HPN-100	NaPBA
Plasma PBA	N=44	N=44
AUC ₀₋₂₄ (µg·h/mL)	433 (76.6)	508 (72.7)
C _{max} (µg/mL)	51.9 (67.2)	80.9 (64.9)
C _{min} (µg/mL)	1.44 (201.2)	0.0905 (392.3)
T _{max} (h) ^a	8.00 (0.00, 15.17)	3.08 (1.52, 12.30)
Plasma PAA	N=43	N=43
AUC ₀₋₂₄ (µg·h/mL)	447 (130.4)	599 (91.6)
C _{max} (µg/mL)	38.5 (102.6)	52.2 (80.2)
C _{min} (µg/mL)	2.11 (381.3)	0.903 (377.7)
T _{max} (h) ^a	11.58 (0.00, 19.27)	8.17 (1.98, 16.08)

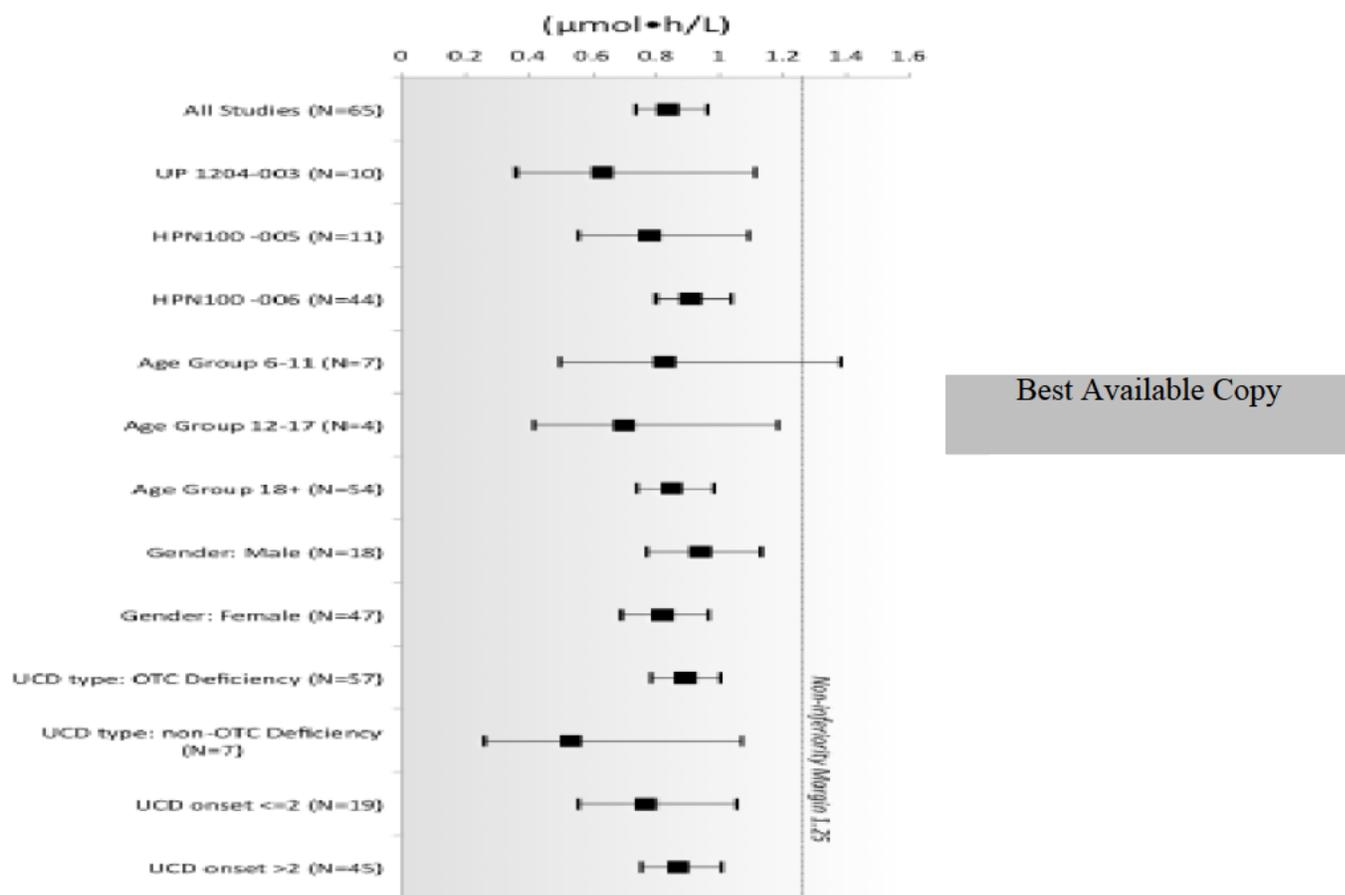
Plasma PAGN	N=44	N=44
AUC0-24 (µg•h/mL)	1127 (61.7)	1252 (57.3)
Cmaxss (µg/mL)	78.6 (55.8)	86.8 (51.5)
Cminss (µg/mL)	15.1 (138.1)	9.09 (154.7)
Tmax (h) a	10.04 (0.00, 20.00)	8.05 (2.00, 16.08)

[Ref: HPN-100-006, Table 26, p.83.]

6.1.7 Subpopulations

With the exception of the age group 6 to 11, in which there were only seven patients, all sub-groups showed that ammonia control was similar between HPN-100 and NaPBA. As Figure 8 shows, subpopulations included age, gender and OTC deficiency.

Figure 8 Analysis of Blood Ammonia AUC across subpopulations



[Ref: Summary Clinical Efficacy, Figure 2.7.3-21, p.110]

Reviewer's Comment:

Although patients 29 days to <6 years (n=15) are not included in the above graph, patients in this age group had similar ammonia control between the two drugs.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing guidelines for Ravicti are based on current dosing for Buphenyl, information from clinical studies in UCD patients, and PopPK analysis. Dosing in UCD patients is determined by a variety of factors: UCD subtype, growth requirements, diet, and severity of urea synthetic defect. The dose of Ravicti used in clinical studies was selected to provide the PBA equivalent dose of NaPBA, and was derived from the following formula:

$$\text{NaPBA (g)} \times 0.864 = \text{daily HPN-100(mL)}.$$

The current label for sodium phenylbutyrate does not recommend actual measurement of PAGN based on the premise that conversion of PBA to PAGN is complete. However PK studies done for this NDA have shown that the amount of residual urea synthetic capacity varies among patients and effects the amount of PBA converted to PAGN. Since the conversion rate of HPN-100 varies among patients the following formula, based on 24-hr urinary excretion of PAGN, is recommended by the sponsor.

(b) (4)

[Ref: ISE, p.118]

As noted, dosing in clinical studies was based on NaPBA dosing since HPN-100 is a pro-drug of PBA and shares the same metabolic pathway as NaPBA. In the application the sponsor states that in the cross-over studies NaPBA withdrawal could be done most safely by giving the equivalent amount of PBA, in the form of HPN-100. Patients not previously on NaPBA were started on the PBA equivalent of the low end of the recommended NaPBA dose range (8.6mL/m²/d), with modification of the dose based on 24-h urinary excretion of PAGN. The sponsor states that 8.6 mL/m²/d dose of HPN-100 would scavenge waste nitrogen derived from approximately 12g of dietary protein with no residual urea synthetic capacity and 60% conversion of HPN-100 to PAGN [Ref: Summary of Clinical Efficacy, p.119].

Dosing proposed for HPN-100 is based on body surface area (BSA) with a dosing range of 4.5 mL/m²/day to 11.2mL/m²/day [5.0g/m²/day to 12.4 g/m²/day]. Total daily dose should not exceed 17.5mL [19.3 g]. This proposed dosing was derived from dosing in UCD patients in Ravicti studies.

Table 18 HPN-100 Proposed Starting Dose

BSA	Recommended Starting Dose
(b) (4)	

[Ref: ISS-120 day, Table 8, p.37]

Pursuant to data from pediatric study HPN-100-012 the starting dose of Ravicti for patients with a BSA of (b) (4)

The sponsor also recommends measuring the ratio of PAA to PAGN rather than PAA alone for therapeutic monitoring. The rationale for this method is that PAA levels are variable in all populations and across different doses; a single measure is difficult to interpret even if drawn at peak levels. The company is proposing that the dose of Ravicti be lowered if the PAA to PAGN ratio is > (b) (4) in a patient with unexplained neurological adverse events and normal ammonia levels.

The PAA to PAGN ratio examines the ability of a patient to convert the precursor PAA, to the final product PAGN. The conversion of PAA to PAGN involves conjugation with glutamine in the liver and kidney, which varies among patients. A high ratio indicates inefficient conversion of PAA to PAGN for reasons such as liver impairment, small body size (since metabolism of PAA to PAGN correlates with body surface area), high dose relative to conversion capacity, or inadequate glutamine precursor.⁶

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Most studies for the NDA were short-term, with duration less than two weeks. Two long-term safety studies have been completed, HPN-100-005SE and HPN-100-007. Safety extension HPN-100-012 is ongoing. In addition to these safety extension studies HPN-100-011 is a treatment protocol consisting of patients who have participated in either HPN-100-005SE or HPN-100-007. All combined, 100 UCD patients have received HPN-100 in long-term open label studies.

HPN-100-005 (Safety Extension):

Of the patients in study 005, eleven had completed the switch-over phase of HPN-100-005 and 6 patients were new. One patient (03-5031) withdrew consent at month 11; the remaining 16 completed the 12-month safety extension. Two patients had deviations in eligibility criteria and both were given an exemption to enroll in the study. One had not been on a stable dose of NaPBA for at least 1 week because she had run out of medication. The other had a history of QTc prolongation (QTc B interval >450 msec at baseline) and abnormal ECGs that were not considered clinically significant.

Three patients had hyperammonemic crises during the study, two of whom had hyperammonemic crisis in the 12 months prior to the study. As Table 19 shows, over the twelve month study duration mean ammonia levels were below the standardized ULN 35µmol/L for all age groups.

⁶ Hyperion Therapeutics: Analysis of Plasma PAA: PAGN Ratio, p.25.

Table 19 HPN-100-005SE Mean (SD) and Maximum Ammonia Levels Over Time

Normalized Ammonia Level* (µmol/L)	6–11 years (N=11)		12–17 years (N=6)		All Patients (N=17)	
	Mean (SD)	Maximum	Mean (SD)	Maximum	Mean (SD)	Maximum
Baseline ^b (n=17)	15.922 (9.2663)	30.46	14.862 (12.6231)	31.11	15.548 (10.1849)	31.11
Month 1 (n=17)	16.953 (11.4115)	37.33	27.331 (21.5270)	64.16	20.616 (15.8852)	64.16
Month 2 (n=13)	13.721 (7.4230)	21.70	30.036 (18.9402)	55.22	19.996 (14.8312)	55.22
Month 3 (n=17)	14.879 (9.2972)	31.50	24.175 (17.9401)	47.00	18.160 (13.2502)	47.00
Month 4 (n=13)	15.923 (8.0092)	28.64	17.978 (11.4107)	34.22	16.556 (8.7344)	34.22
Month 5 (n=15)	26.261 (23.9176)	69.56	23.448 (14.2799)	39.00	25.136 (20.0436)	69.56
Month 6 (n=16)	22.989 (22.2113)	81.19	23.121 (15.0785)	44.00	23.031 (19.7365)	81.19
Month 7 (n=14)	22.496 (22.7418)	84.05	21.118 (16.4078)	44.58	22.102 (20.5085)	84.05
Month 8 (n=17)	21.165 (18.9510)	70.53	21.729 (12.1613)	41.00	21.364 (16.4547)	70.53
Month 9 (n=16)	17.849 (10.8700)	36.17	38.778 (36.2781)	97.00	25.698 (24.8817)	97.00
Month 10 (n=14)	15.879 (12.7348)	42.13	16.346 (2.3787)	19.38	16.013 (10.6597)	42.13
Month 11 (n=14)	16.554 (13.4220)	48.35	35.065 (23.9385)	62.74	23.165 (19.2849)	62.74
Month 12 (n=15)	17.689 (19.2143)	61.83	21.758 (13.9385)	44.00	19.045 (17.2275)	61.83

[Ref: HPN-100-005se CSR, Table 13, p.53]

HPN-100-012 (Safety Extension):

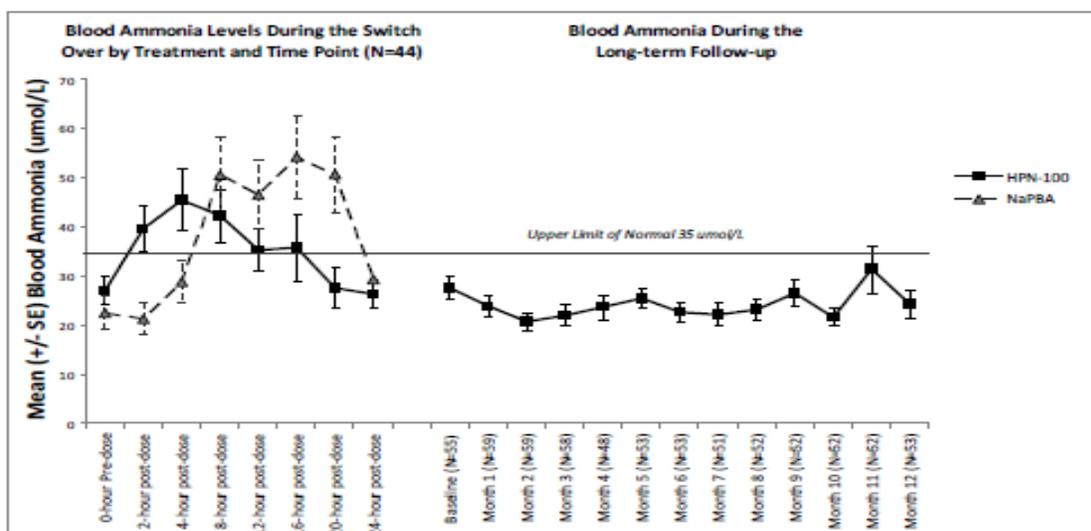
This ongoing study is designed to evaluate long-term safety, and ammonia control of HPN-100 in UCD patients ages 29 days to <6 years. Fifteen patients participated in the switch over study (HPN-100-012) and an additional 7 patients enrolled directly. As of March 2012 no patients have discontinued the study. The median exposure is 3.5 months.

Three pediatric patients experienced a total of four hyperammonemic events. One event was precipitated by gastroenteritis, and resulted in an ammonia level of 166. A second event in the same patient was associated with an upper respiratory infection and decreased oral intake. The ammonia level on hospital admission was 182 µmol/L. The third event was precipitated by vomiting, and was associated with an ammonia level of 156 µmol/L. The fourth event in a 4-month old patient was precipitated by an upper respiratory infection, with an ammonia level of 116 µg/dL. In each case the hyperammonemia was precipitated by intercurrent illness.

HPN-100-007 (Safety Extension):

This twelve month study enrolled sixty patients, nine of whom were ages six to seventeen. Ammonia levels were measured at baseline, and then monthly. Mean ammonia levels were all within the upper limit of normal of 35 $\mu\text{mol/L}$. Figure 9 shows that during the 24-hour switch over mean ammonia levels fluctuated for both HPN-100 and NaPBA (with higher levels for NaPBA). During the twelve month period of the safety study the mean ammonia level at each month was below the upper limit of normal.

Figure 9 HPN-100-007 Mean Ammonia Levels over Time



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[Ref: HPN-100-007, Figure 3, p.60.]

During the study 12 hyperammonemic crises occurred in nine patients (7 adults, 2 children age 6-11). The most common causes were intercurrent illness or noncompliance.

Table 20 HPN-100-007 On-study Hyperammonemic Crises

	6–11 years (N=6)	12–17 years (N=3)	≥ 18 years (N=51)	All Patients (N=60)
Patients with ≥ 1 hyperammonemic crisis,^a n (%)	2 (33%)	0	7 (14%)	9 (15%)
Number of crises (per patient)				
Mean (SD)	0.33 (0.516)	0.00 (0.000)	0.20 (0.530)	0.20 (0.514)
Median	0.00	0.00	0.00	0.00
Min, Max	0.0, 1.0	0.0, 0.0	0.0, 2.0	0.0, 2.0
Number of crises	2	0	10	12
Precipitating factors, n (%) of total N of crises				
Change in diet	0	0	1 (10%)	1 (8%)
Infection	1 (50%)	0	0	1 (8%)
Intercurrent illness	0	0	5 (50%)	5 (42%)
Noncompliance with study drug	0	0	4 (40%)	4 (33%)
Other ^b	1 (50%)	0	3 (30%)	4 (33%)
None	1 (50%)	0	3 (30%)	4 (33%)
Clinical symptoms,^c n (%) of total N of crises				
Abnormal neurological examination	0	0	1 (10%)	1 (8%)
Chronic migraine headaches	0	0	2 (20%)	2 (17%)
Episodic lethargy	1 (50%)	0	4 (40%)	5 (42%)
Recurrent vomiting	1 (50%)	0	4 (40%)	5 (42%)
Other ^d	1 (50%)	0	7 (70%)	8 (67%)
None	0	0	1 (10%)	1 (8%)
Ammonia at admission^e (μmol/L)				
Mean (SD)	152.50 (4.950)	N/A	143.70 (53.653)	145.17 (48.675)
Median	152.50	N/A	137.00	152.00
Min, Max	149.0, 156.0	N/A	50.0, 239.0	50.0, 239.0

[Ref: HPN-100-007, Table 14, p.62.]

HPN-100-011 Treatment Protocol:

Sixty-seven UCD patients enrolled into this ongoing open-label safety study after completing either HPN-100-005SE or HPN-100-007. As of the cut-off date of 09 Sept 2011 six patients have had 7 serious adverse events of hyperammonemia. Precipitating causes include pancreatitis, decreased oral intake, upper respiratory disorder and seizure.

Table 21 HPN-100-011 Treatment Emergent Serious Adverse Events

Patient	Age (y)/ Sex/Race (UCD Type)	AE Term	Related	Onset Day ^a (Duration)	Serious Criteria	Outcome
01-117606	54/F/W (OTC)	Back Pain	No	14 (2 d)	Hospitalization	Resolved
02-117601	33/F/W (OTC)	Hyperammonemia (G2)	No	90 (2 d)	Hospitalization	Resolved
		Pancreatitis (G2)	No	96 (126 d)	Hospitalization	Resolved
		Hyperammonemia (G2)	No	225 (3 d)	Hospitalization	Resolved
03-115032	18/F/W (OTC)	Hyperammonemia (G3)	No	221 (1 d)	Hospitalization	Resolved
		Hyperammonemia (G3)	No	265 (1 d)	Hospitalization	Resolved
05-117605	29/F/W (OTC)	Hyperammonemia (G3)	No	46 (1 d)	Hospitalization	Resolved with Sequelae
		Hypocapnea (G3)	Possibly	45 (4 d)	Hospitalization	Resolved
		Seizure (G3)	No	52 (1 d)	Hospitalization	Resolved
07-115071	14/F/A (ASL)	Hyperammonemia (G2)	No	23 (1 d)	Hospitalization	Resolved
11-117607	39/M/W (OTC)	Hyperammonemia (G3)	No	42 (1 d)	Hospitalization	Resolved

[Ref: HPN-100-011, Table 4, p. 14.]

Reviewer's Comment:

The purpose of the foregoing analysis was to examine how well ammonia levels are controlled long term by Ravicti. In each safety extension study there were patients who developed hyperammonemia and required acute management. This is not unexpected in UCD patients in which ammonia levels are variable, and affected by illness, diet, or any other catabolic state. Prior to entering the Ravicti trials patients experienced hyperammonemic events while taking Buphenyl. Although Ravicti is non-inferior to Buphenyl in controlling blood ammonia levels, patients with UCDs will always require close monitoring by family and health care providers.

6.1.10 Additional Efficacy Issues/Analyses
No additional issues.

7 Review of Safety

7.1 Methods

The original NDA submission contains safety data for UCD patients aged 6 years and above. At the time of the 120-day safety update, the sponsor provided additional clinical data on 15 patients aged 29 days to six years. Because the pediatric data were submitted late, they were not fully integrated into the NDA submission. This reviewer will attempt to integrate all data, but some tables from the application will not have the later studies included. Adverse events in the thorough QT study (tQT) and study of hepatically impaired subjects will be discussed when they add information about the overall safety profile of the product.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 3, section 5.1 of this review provides a table of clinical studies used to evaluate safety.

7.1.2 Categorization of Adverse Events

Coding using both verbatim and preferred terms appears to be consistent and appropriate.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The method of pooling data was based on study population and study design. Four patient populations are analyzed: UCD patients in short-term studies, UCD patients in long-term studies, healthy volunteers, and hepatically impaired patients.

7.2 Adequacy of Safety Assessments

Assessments in short-term trials were adequate for this rare disease, where available patients to study are limited. In the short-term cross-over studies patients were followed while on Buphenyl, and switched to Ravicti. Pharmacokinetic data were collected, and

the two populations compared at drug steady state. In the long-term safety studies PK data were not always obtained, and therefore PAA levels are not always available in association with adverse events. However, serum ammonia levels were consistently obtained. Overall patients tolerated the switch from Buphenyl to Ravicti. The number of adverse events was small, there were no SAEs, and PAA levels (when available) were below toxic levels.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In most studies conducted for this application patients were switched directly from sodium phenylbutyrate to Ravicti. The dose of Ravicti was the PBA mole equivalent of the Buphenyl dose. In pediatric patients in study 012 doses of Ravicti ranged from 0.8 mL/day to 7.8mL/day, with a median dose of 4.5mL/day. All subjects were switched from NaPBA to HPN-100 in a single transition step beginning on Day 2. They returned to the clinic after 4 to 10 days on HPN-100 for 24-hour blood sampling. After that they continued in the long-term treatment phase. No adjustment to the dose or schedule of HPN-100 was allowed during the switch-over period.

7.2.2 Explorations for Dose Response

In a few instances, in long range safety studies, treatment naïve patients were enrolled without prior NaPBA treatment. In that situation patients were started on a low dose of HPN-100 based on their urea synthetic capacity, ammonia level, diet, and particular enzyme deficiency. Measurement of U-PAGN is important to determine the percentage conversion of administered dose of PBA to PAGN since this varies from patient to patient. In short term cross-over studies fasting ammonia was predictive of ammonia levels over the subsequent 24 hour period. A fasting ammonia level less than half the ULN were found to be associated with a better than 80% likelihood that the average ammonia levels over the next 24 hours will be normal.

7.2.3 Special Animal and/or In Vitro Testing

The non-clinical program was adequate to explore adverse events seen in HPN-100 studies. Rats and monkeys were the primary species used in the toxicology studies. The monkey was the most relevant model due to metabolism similar to humans. There were no unexpected toxicities associated with chronic oral administration of the prodrug GPB, or with exposures to the active metabolites, which were at least 4-fold higher than therapeutic exposures in UCD patients.

Because of concern about potential side effects associated with metabolite levels of HPN-100, the PK of the drug in monkeys was investigated. PK and metabolism studies in monkeys showed that PBA is absorbed more slowly from the GI tract after dosing with GPB compared to PBA. The AUC₀₋₂₄ (2204-2795 µg·h/mL) of PAA at the NOAEL level (1.1 g/kg/day (13.2 g/m²/day)) for males and females in the chronic monkey study

was approximately 4-fold higher than the steady-state PAA exposure seen in adult UCD patients (447 µg·h/mL) in study 006. The sponsor postulates that because monkeys do not have a nitrogen retention state, or elevated levels of glutamine that are present in UCD patients they do not need the higher doses of PBA of UCD patients.

7.2.4 Routine Clinical Testing

Routine clinical testing involved measurement of ammonia, metabolites, and measurement of amino acids. These measurements were done on a schedule in each study. Certain testing was also done as-needed, in the event of an adverse event. In addition to scheduled laboratory testing, physical exams and vital signs were monitored.

7.2.5 Metabolic, Clearance, and Interaction Workup

Further detail concerning metabolism, clearance and drug-drug interactions can be found in the FDA Clinical Pharmacology review.

Metabolism. The metabolic pathway of HPN-100 has been discussed earlier in this review.

Clearance. No intact HPN-100 was detected in pre-clinical or clinical studies confirming that the drug is completely hydrolyzed in the gut lumen before any intestinal absorption occurs.

Interactions. No in vivo drug-drug interaction (DDI) studies were conducted. In vitro studies indicate that intestinal lipases are the key enzymes responsible for the hydrolysis of HPN-100.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
Buphenyl has the same active drug/active metabolite as Ravicti, so adverse events seen with Ravicti would be seen with Buphenyl, and vice versa. Overall no major safety signals have been seen with either drug, but potential toxicity with exposure to the active metabolite PAA remains a concern. The positive findings in Carcinogenicity studies of HPN-100 (see section 4.3 Clinical Review) also apply to Buphenyl. No carcinogenicity studies were performed during development of Buphenyl.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in UCD patients in the short-term controlled studies, the long-term open-label studies, or the ongoing treatment protocol. The only deaths seen in patients receiving HPN-100 were in non-UCD patients with hepatic impairment.

Reviewer's Comment:

No UCD patient died in any HPN-100 study. The deaths in cirrhotic patients with episodic encephalopathy all related to their underlying liver disease and co-morbid medical conditions.

7.3.2 Nonfatal Serious Adverse Events

SAEs and TESAEs are considered together. Also, the reader is referred to section 6.1.9, where the SAE of hyperammonemia is discussed in the context of persistence of efficacy of Ravicti. In Study 006 and in cross-over studies a direct comparison between Buphenyl and Ravicti with regard to serious adverse events was made. Study 006 allowed for a head to head comparison between the two drugs since patients were on Ravicti and active control for 2 weeks each. In the other cross-over studies minimal comparative data is available because patients were switched to HPN-100 within the first few days of the study.

Treatment emergent serious adverse events (TESAE) occurred in 3 of 70 (4.3%) patients with UCDs in short-term trials. One patient (trial HPN-100-006) had acute gastroenteritis while receiving HPN-100. Two patients (in UP1204-003 and HPN-100-006) had Grade 3 hyperammonemia while receiving NaPBA. TESAEs occurred in 15 of 77 (19.5%) patients in long-term open label safety extension studies. The most common TESAE was hyperammonemia, reported in 11 patients (14 events). Other TESAEs were gastroenteritis (2), aggression, abdominal pain, dizziness, lobar pneumonia, lung infiltration, peripheral neuropathy, psychotic disorder, and pelvic pain.

In pediatric cross-over study HPN-100-012 there were no TESAEs; as of 1-MAR-12 three patients in the safety extension study had a treatment emergent serious adverse event. A four year old patient had two episodes of hyperammonemia (grades 2 & 3) that resolved. A five month old patient had one episode of hyperammonemia, and a 4 month old patient had an episode of poor feeding.

In treatment protocol HPN-100-011 six patients were reported with TESAEs in the original NDA, and 6 more were added in the 120-day safety update. As Table 22 shows, the most frequent TESAE in treatment protocol HPN-100-011 was hyperammonemia.

Table 22 HPN-100-011 Serious Adverse Events as of 01 March 2012

System Organ Class Preferred Term	Number (%) of Patients	
	Total as of 09 Sept 2011	Total as of 01 March 2012
	N=67	N=67
Any TESAE	6 (9.0%)	12 (17.9%)
Metabolism and nutrition disorders		
Hyperammonaemia	5 (7.5%)	17 (25.4%)
Hypokalaemia	0	1 (1.5%)
Hyponatraemia	0	1 (1.5%)
Nervous system disorders		
Seizure/convulsion	1 (1.5%)	1 (1.5%)
Gastrointestinal disorders		
Pancreatitis	1 (1.5%)	1 (1.5%)
Abdominal pain		1 (1.5%)
Nausea	0	1 (1.5%)
Respiratory, thoracic & mediastinal disorders		
Hypocapnea	1 (1.5%)	1 (1.5%)
Diffuse chronic bronchitis	0	1 (1.5%)
Musculoskeletal and connective tissue disorders		
Back pain	1 (1.5%)	1 (1.5%)
Injury, poisoning and procedural complications		
Spinal compression fracture	0	1 (1.5%)
Uncoded		
Dehydration	0	1 (1.5%)

[Ref: 120-day Safety Update, Table 13, p.47]

Reviewer’s Comment:

With the exception of pivotal study HPN-100-006, the opportunity for comparisons of AEs between drugs is limited. The Buphenyl label states that adverse events were not collected systematically in treated patients, and that the events were reported primarily by parent of guardian. Therefore the TESAEs seen in long-term studies for Ravicti are frequently not the same as the clinical AEs listed in the Buphenyl label. The Buphenyl label states that “causality of adverse effects is sometimes difficult to determine in the patient population because they may result from either the underlying disease, the patient’s restricted diet, intercurrent illness, or Buphenyl.”⁷

7.3.3 Dropouts and/or Discontinuations

In the short-term studies with NaPBA control 85 patients comprise the safety population (70 in the original NDA and 15 from HPN-100-012). Seven patients withdrew from short-term studies: 2 for AEs, 2 for withdrawn consent, 2 for “other” reasons, and 1 per request of investigator. One patient listed as “other” was withdrawn due to failure to return to the study site. The patient was later re-enrolled under a different identifier, and ultimately asked to withdraw at the request of the investigator before receiving any study medication. The two withdrawals due to adverse events were in patients receiving

⁷ Buphenyl (sodium phenylbutyrate) Human Prescription Drug Label. Adverse Reactions.

sodium phenylbutyrate: one was due to a high blood ammonia level and headache, and the other due to hyperammonemia.

In long-term open-label studies eight patients were listed as withdrawn at the time of the NDA submission. Two additional patients were added in the 120-day safety update. One patient withdrew due to an elective liver transplant, seven due to withdrawal of consent, one due to investigator discretion because the patient relocated outside the US, and one due to an adverse event.

Patient 18-7624, rolled over from trial 006. She had multiple TEAEs after 106 days of treatment in the safety extension. At month 2 she had a dose reduction from 18 to 16 mL/day due to moderate vomiting. The patient also experienced lethargy, dizziness, confusion, speech disorder and tremors. She had one elevated ammonia value (65 µmol/L) at month one. No PAA concentration data were obtained since PK was not required as part of the protocol.

Patient 07-7714 was a 41 year old Asian female newly enrolled into Study 007. She had 30 TEAEs before withdrawing consent, some of which were neurological TEAEs (headache, dizziness, somnolence, and tremor). Her dose of Ravicti was reduced from 17.4 to 9 mL/day for Grade 2 headache and paresthesia. She stayed on the drug for 11 weeks longer, but continued to have TEAEs. The patient withdrew consent after 72 days of treatment; one of the reasons for doing so was TEAEs considered possibly related to study treatment. All ammonia values for this patient were normal, and all PAA levels were BLQ.

Reviewer's Comment:

No patients in pediatric safety extension study 012 have withdrawn as of 01 March 2012. The two patients discussed above had dose reductions. Patient 07-7714 was treatment naïve when she entered study 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 BLQ. Patient 18-7624 also had a dose reduction due to vomiting. No PAA levels were obtained for her.

QT study in Healthy Volunteers

Thorough QT study HPN-100-010 is discussed because of a large number of AEs and discontinuations due to Adverse Events. In arm one, conducted to determine a supratherapeutic dose (9mL TID or 12 mL TID), 10 of 12 subjects completed the study. One subject withdrew due to the AE of vomiting and the other due to withdrawal of consent. Eighty-six subjects enrolled in arm 2, out of which eighteen subjects discontinued due to an adverse event: 14 in the HPN-100 arm(s) and 4 in the placebo arm.

The largest numbers of discontinuations (7) were in subjects receiving 6mL Ravicti. The majority of subjects withdrew due to headache or nausea/vomiting. The rate of discontinuations due to an AE was similar in placebo (4.8%) and 4 mL (4.4%) 3 times

per day dose groups and increased with higher doses of HPN-100. Subjects receiving 9 mL (TID) were more likely to drop out of the study (33.3%) followed by those who received 12 mL (25.0%) and 6 mL (9.3%). Below is a listing of the nineteen subjects who discontinued study drug due to adverse events.

Placebo:

- subject 023 – mild headache, upper abdominal pain and tenderness, moderate photophobia and nausea
- subject 034 – upper respiratory tract infection and otitis media
- subject 041 – moderate headache
- subject 053 – mild retching

4 mL HPN-100:

- subject 065 – mild irritability, sleep disorder, fatigue, moderate depressed mood
- subject 068 – moderate nausea, abdominal discomfort, headache
- subject 158 – moderate headache and nausea

6 mL HPN-100:

- subject 015 - mild platelet count decreased (139 thousand/ μ L at screening, 114 thousand/ μ L period 5, day 4)
- subject 037 - moderate nausea
- subject 040 - mild/moderate headache; mild abdominal pain, tremor, and dizziness; and moderate vomiting, nausea, and asthenia
- subject 070 - mild flushing and moderate nausea and headache
- subject 071 - moderate headache
- subject 072 - mild asthenia and nausea
- subject 126 - pneumothorax on day 20 (history of smoking)

9 mL HPN-100:

- subject 025 – mild dizziness, moderate nausea, severe headache
- subject 033 – moderate headache and photophobia
- subject 038 – severe dizziness
- subject 042 – mild headache and moderate nausea

12 mL HPN-100:

- subject 012 - moderate vomiting day 4, 2 hours after receiving second daily dose

Many of the adverse events were headache or nausea/vomiting. The rate of neurological TEAEs increased with higher doses. Table 23 shows that the highest percentage of patients with neurologic adverse events was in the 9mL TID arm.

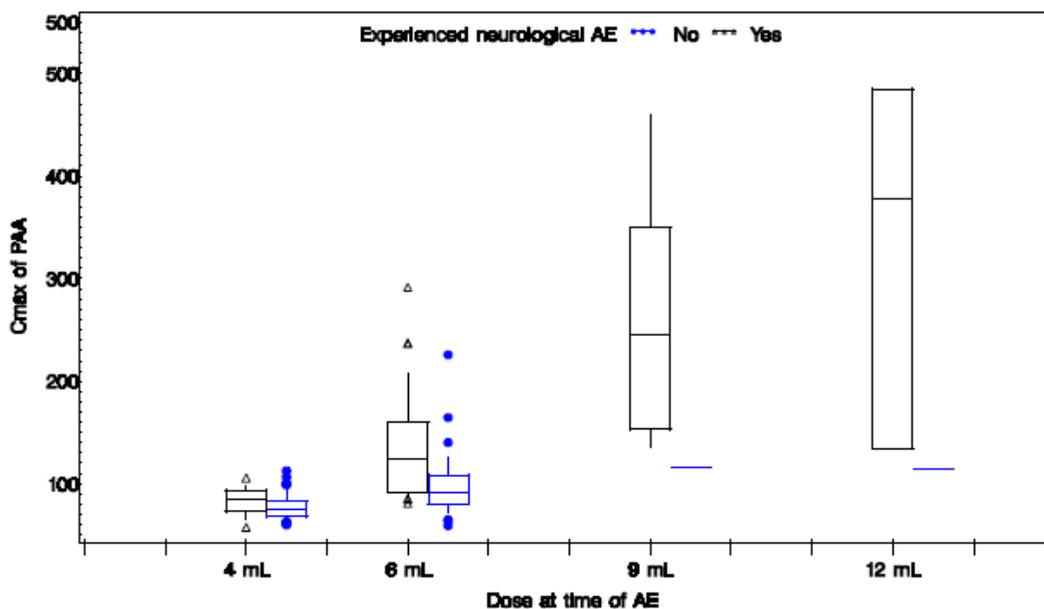
Table 23 Percentage of Patients with Neurologic Adverse Events

N	Placebo	Moxifloxacin 400 mg	HPN-100 4 mL	HPN-100 6 mL	HPN-100 9 mL	HPN-100 12 mL
Exposed	84	77	68	75	12	4
Nervous system disorder AE	8	6	18	35	11	3
Percent	9.5%	7.8%	26.5%	46.7%	91.7%	75.0%

[Ref: Clinical Study Report HPN-100-101, Table 12-11, p.178]

A key question is whether PAA levels were elevated at the time of the neurologic symptoms. Figure 10 shows that as the dose of HPN-100 goes up so does the Cmax of PAA, and the incidence of neurologic AEs. The greatest number of neurological AE occurred at the 12 mL dose.

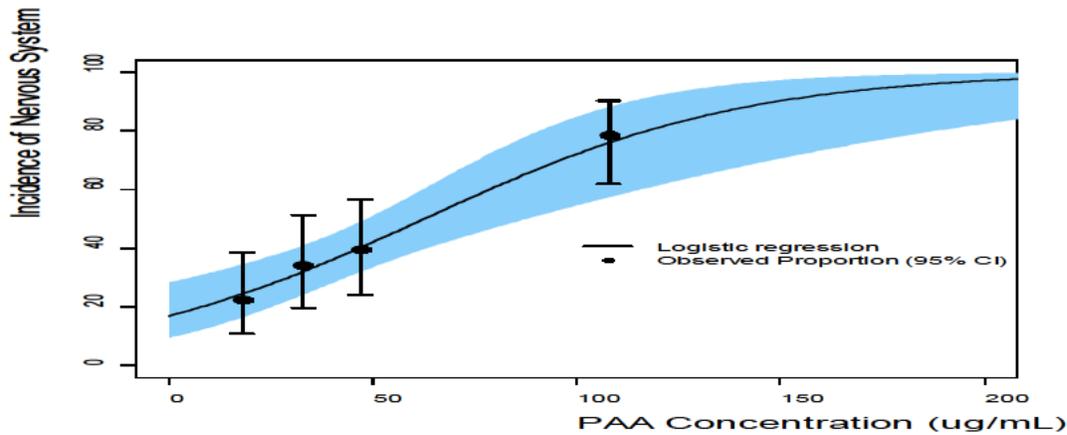
Figure 10 Cmax of PAA in Subject with and Without TEAE of Nervous System



[Ref: Clinical Study Report, HPN-100-010, Figure 12-2, p.179]

Figure 11 and Figure 12 explore the relationship between nervous system disorders and PAA levels in the QT study, and in UCD patients enrolled in clinical trials for the Ravicti, respectively. In the QT study as the dose of Ravicti was increased in healthy volunteers, the PAA level, and the incidence of neurologic adverse events increased (Figure 11). This same pattern was not seen in UCD patients (Figure 12).

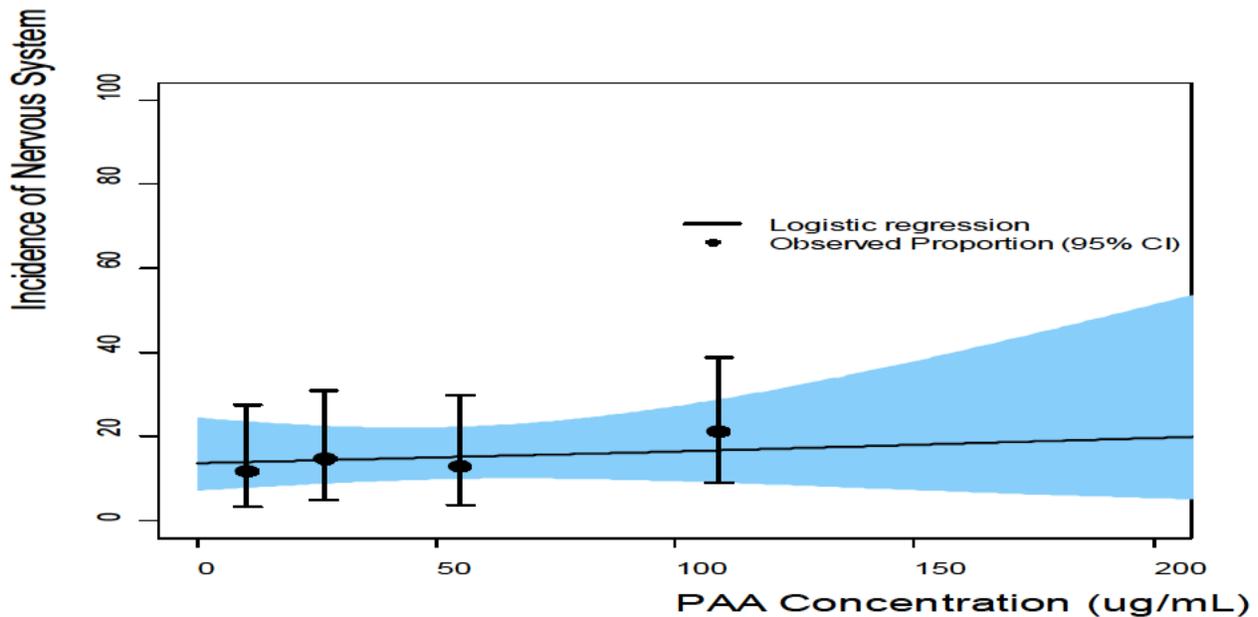
Figure 11 PAA levels and dose tQT study



4 mL (n=68), 6 mL (n=45), 9 mL (n=12), 12 mL (n=4)

[Ref: Dr. Kevin Krudys, FDA Reviewer, Office of Clinical Pharmacology]

Figure 12 PAA levels and nervous system disorders UCD patients



[Ref: Dr. Kevin Krudys, FDA Reviewer, Office of Clinical Pharmacology]

Reviewer's Comment:

As stated in the proposed Ravicti label, the total daily dose is not to exceed 17.5mL. At this dose the PAA levels reached in the tQT study were under 100. In addition, as Figure 12 shows, in actual UCD patients there does not appear to be a relationship between PAA levels and nervous system adverse events.

7.3.4 Significant Adverse Events

No SAEs are discussed in this section since they are addressed elsewhere in this review.

7.3.5 Submission Specific Primary Safety Concerns

As discussed in section 4.4, Ravicti is a pre-prodrug that is broken down into the active drug/metabolite PAA. Although no specific adverse events have been linked to PAA in HPN-100 studies, it remains a topic requiring further discussion, particularly with regards to pediatric patients.

In meetings with the sponsor prior to submission of the NDA, the FDA expressed concern about potential toxicity associated with PAA. Phenylacetic acid is an endogenous chemical involved in the catabolism of phenylalanine, and the active metabolite of both NaPBA and HPN-100. At elevated levels PAA can be neurotoxic. The manifestations of PAA toxicity mimic those of hyperammonemia, and include nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, and other CNS effects. Therefore UCD patients taking NaPBA or HPN-100 who present with signs of hyperammonemia may be experiencing effects of PAA toxicity. Obtaining an ammonia level is necessary because, if elevated, it may explain the patient's symptoms. However, even with an elevated ammonia level, PAA toxicity cannot be ruled out entirely since it is possible that the two conditions could occur simultaneously. Treating symptoms thought to be due to hyperammonemia, but actually due to PAA toxicity, could be hazardous to the patient because the treatment of hyperammonemia is administration of a nitrogen scavenging drug that breaks down into PAA.

The NDA submission contains published accounts⁸ of adverse events occurring in cancer patients receiving intravenous PAA (250-300 mg/kg/day for 14 days, repeated at 4-week intervals) associated with peak plasma PAA concentrations ranging from 499-1285 µg/mL. In an article by Simell et al⁹ the safe upper PAA concentration limit was calculated to be 3.5 mM (476 µg/m). The most common manifestations of PAA toxicity in Oncology patients were somnolence, fatigue, and lightheadedness, but some patients also experienced headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of pre-existing neuropathy. These adverse reactions were reversible when the PAA infusion was discontinued.

Table 24 shows the PK parameters of PAA for NaPBA and HPN-100 in adult and pediatric patients in UCD trials. This table shows that the highest mean PAA concentration reported in the four studies was 98µg/mL (in a patient receiving NaPBA), well below the range reported in the literature as being potentially toxic (499-1285 µg/mL). This table also shows that for both drugs pediatric UCD patients had higher

8 Thibault A, et al. A Phase 1 and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer. *Cancer Research* 54: 1690-1694, 1994.

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

mean exposure and concentration than adult UCD patients. While PAA levels for HPN-100 compared to NaPBA were higher in the older children (≥ 6 years), the opposite is the case in the youngest patients. For the fifteen patients 29 days to 6 years AUC_{0-24} , C_{max} and C_{min} were higher with NaPBA compared to HPN-100.

Table 24 PK of HPN-100 and NaPBA in Adult and Pediatric UCD Patients

PK Variable	Adult UCD Patients (≥ 18 years)				Pediatric UCD Patients (29days – 17 years)			
	UP1204-003 (n=10)		HPN-100-006 (n=44)		HPN-100-005 (n=11) (6 years – 17 years)		HPN-100-012) n=15 (29 days – 6 years)	
	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA	HPN-100	NaPBA
Mean (SD) Dose	12.3 (3.91)	12.6 (4.11)	12.50 (5.529)	12.33 (5.582)	11.04 (3.859)	10.94 (3.873)	5.16 (2.316)	5.27 (2.453)
Plasma PAA								
AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	574.6 (168.9)	595.6 (123.9)	447 (130.4)	599 (91.6)	964 (63.6)	773 (73.3)	1096 (214.0)	1458 (211.3)
C_{max} ($\mu\text{g}/\text{mL}$)	40.5 (147.6)	53.0 (94.7)	38.5 (102.6)	52.2 (80.2)	90.5 (69.1)	75.1 (64.4)	84.7 (148.3)	98.0 (152.1)
C_{min} ($\mu\text{g}/\text{mL}$)	7.06 (310.7)	3.56 (194.4)	2.11 (381.3)	0.903 (377.7)	2.99 (122.1)	0.674 (130.5)	26.1 (360.8)	49.2 (287.2)

[Ref: adapted from 120-day safety update, Table 2, p.19.]

In pediatric study HPN-100-012SO the blood levels of PAA are obtained on day 1 for NaPBA and day 10 for HPN-100. These time points represent steady state for each drug. As these data show (Table 25) the highest PAA concentration for Ravicti was 480 $\mu\text{g}/\text{mL}$, and the highest PAA concentration for Buphenyl was 530 $\mu\text{g}/\text{mL}$. Thus the highest PAA concentrations in Ravicti studies were in pediatric patients.

Table 25 PK Parameters of PAA at Steady State for NaPBA and HPN-100

PK Parameters of PAA in Plasma										
Subject	NaPBA (Day 1)					HPN-100 (Day 10)				
	AUC ₀₋₂₄ (µg·h/mL)	CL _{ss} /F (mL/h)	C _{max,ss} (µg/mL)	C _{min,ss} (µg/mL)	T _{max,ss} (h)	AUC ₀₋₂₄ (µg·h/mL)	CL _{ss} /F (mL/h)	C _{max,ss} (µg/mL)	C _{min,ss} (µg/mL)	T _{max,ss} (h)
01-1212 ^a	133.6	40960	37.9	<1.000	12.00	398.8	13998	52.4	<1.000	8.00
02-1203	27.55	145650	7.52	<1.000	7.33	78.76	51541	20.8	<1.000	7.58
02-1208	2352	2327	205	5.73	6.50	2301	2425	207	9.84	7.42
04-1202	264.7	14061	41.7	<1.000	8.50	854.7	4453	93.3	1.07	8.00
04-1207	34.45	63542	4.98	<1.000	7.58	306.4	7452	37.5	<1.000	8.45
05-1209	11130	203	530	520	8.00	-	-	-	-	-
05-1210 ^a	4783	1220	286	148	8.00	8979	678	480	354	8.83
05-1213	154.0	25392	18.5	<1.000	8.00	54.74	74157	7.43	<1.000	8.00
10-1214 ^b	-	-	-	-	-	6.956	97269	3.48	<1.000	12.00
11-1201	462.4	14202	69.6	<1.000	11.83	530.2	12442	72.9	<1.000	8.00
11-1204 ^a	359.8	9125	43.6	<1.000	7.78	263.1	13499	33.6	<1.000	7.78
11-1206	63.34	103678	14.4	<1.000	12.17	392.7	16799	43.2	<1.000	7.83
11-1211	157.8	15254	14.1	14.1	8.10	58.12	43656	7.73	<1.000	8.17
16-1205	3.323	878197	1.77	<1.000	11.93	185.3	16435	27.4	<1.000	7.75
16-1215	479.9	5474	76.8	<1.000	7.88	930.3	2727	99.3	1.39	7.63

<1.000 =below limit of quantification

^A Subjects 11-1211, 05-1210 and 11-1204 received NaPBA via G-tube and HPN-100 orally

^B Subject 10-1214 had concentrations below the LOQ at all-time points following NaPBA treatment
 [Ref: HPN100-012 PK Report, Table 9.5, p.32.]

A critical question is whether there were adverse events associated with higher PAA concentrations. An examination of adverse events for the 10 day cross-over study shows that there were no serious adverse events, no changes in dose, and at the highest PAA levels no obvious neurological signs or symptoms.

Table 26 shows each adverse event in the short-term cross-over study HPN-100-012. There were no adverse events reported in patients while on Buphenyl, since they were switched to Ravicti on day 2. The PAA C_{max} for Ravicti and Buphenyl listed in the table were obtained at steady state for each drug (day 1 for Buphenyl and Day 10 for Ravicti). They are added to the table for informational purposes, and correlate adverse event with PAA level. In all but two patients the PAA C_{max} for both drugs were low. Only patient 05-1210 and patient 05-1209 had a PAA level over 100, and each experienced only grade 1 adverse events.

Table 26 Adverse Events HPN-100-012 Switch-Over

Patient	Adverse Event	CTCAE Grade	Action taken with study drug	PAA Cmax Ravicti (µg/mL)	PAA Cmax Buphenyl (µg/mL)
05-1210	Vomiting	1	Dose not changed	480	286
05-1213	Respiratory Infect.	1	Not applicable	7.43	18.5
10-1214	Heart Murmur	1	Dose not changed	3.48	Below LOQ
11-1201	Abd.Discomfort, nausea	2	Not applicable	72.9	69.6
16-1215	Papule	1	Dose not changed	99.3	76.8
01-1212	Vomiting x 4	1	Dose not changed	52.4	57.9
04-1202	Lymphadenopathy	1	Dose not changed	93.3	41.7
05-1209	Flatulence	1	Dose not changed	Below LOQ	530

[Ref: adapted from HPN100-012 Switch over Analysis, Listing 16.2.7.1, p.2-3 and HPN100-012 PK Report, Table 9.5, p.32.]

At the time of the cross-over study patient 05-1210 was a 1-year old boy with neonatal onset ASS deficiency. The patients had recurrent vomiting most of the time after receiving NaPBA through a G-tube. The vomiting increased on day 5 after receiving HPN-100 orally and resolved on Day 6. The sponsor notes that on day 10 the vomiting was still present, but improved from screening. The child's the ammonia level was 110 µmol/L while receiving NaPBA, and 31 µmol/L while receiving HPN-100. No adverse events have been reported for this patient in the safety extension study.

Because all patients in the cross-over study enrolled in the safety extension, it is possible to continue to follow them. Patient 05-1209 for example, was 2 months old at the time of the cross-over study and had the highest PAA concentration (530µg/mL) on day one hour eight of Buphenyl dosing. No corresponding PAA level while on Ravicti was available, and in the cross-over study no adverse events were reported. Going forward into the safety extension study the patient had multiple AEs, all except one graded as mild.

Table 27 AEs subject 05-1209.

Subject Identifier	System Organ Class/ Reported AE Term	CTCAE Grade: Severity	Serious AE	AE Start Date	AE Stop Date	Action Taken with Study Drug	Outcome of Adverse Event
05-1209	Gastrointestinal disorders/ Increased gas	Grade 1: Mild AE	No	2011-11-04		No action taken	Not recovered
	Gastrointestinal disorders/ Increased vomiting	Grade 1: Mild AE	No	2011-12-12	2011-12-27	No action taken	Recovered
	Gastrointestinal disorders/ Increased vomiting	Grade 1: Mild AE	No	2012-01-16	2012-02-02	No action taken	Recovered
	Metabolism and nutrition disorders/ Decreased PO intake	Grade 1: Mild AE	No	2012-01-16	2012-02-09	No action taken	Recovered
	Metabolism and nutrition disorders/ Poor feeding	Grade 3: Severe AE	Yes	2011-12-19	2011-12-22	No action taken	Recovered
	Skin and subcutaneous tissue disorders/ Dermatitis on right cheek	Grade 1: Mild AE	No	2012-01-23	2012-02-23	No action taken	Recovered
	Infections and infestations/ Upper respiratory infection	Grade 1: Mild AE	No	2011-11-29		No action taken	Not recovered

[Ref: HPN-100-012 Abbreviated Clinical Study Report, Listing 1, p.43.]

The patient's medical history includes argininosuccinate synthetase (ASS) deficiency, patent foramen ovale, and grade 2/4 systolic heart murmur. The patient had one hyperammonemic crisis in the 12 months prior to study entry. The Grade 3 SAE of reduced oral intake was preceded by an upper respiratory infection that resulted in decreased oral intake and vomiting, leading to weight loss and essential amino acid deficiencies. She had an ammonia level of 116µg/dL. She was admitted to the hospital for nutritional management and nasogastric tube placement. After that she began to improve and her ammonia normalized to 39 µg /dL. No PAA level was available.

The other two youngest subjects were 11-1211, an 11 month-old with a PAA level of 14µg/mL, and 16-1215, a one-year old with a PAA of 99µg/mL. Subject 11-1211 had a mild AE of conjunctivitis, and subject 16-1215 had an erythematous papule on the chest.

Reviewer's Comment:

Although the safety extension study is still ongoing, neurologic adverse events such as those described by Thibault in the Oncology patients are not reported. In the very youngest and vulnerable group under the age of two there is no evidence of neurologic adverse events suggestive of PAA toxicity. In long-term safety extension studies PK data were obtained less frequently than in the short-term studies. For example for HPN-100-006 and HPN-100-005SE PK data were added to the blood samples drawn for amino acid analysis at month 0, 3, 6, 9 and 12. In HPN-100-012 these data are planned for baseline, week 1, and months 1,2,3,6 and 12.

Table 28, from the original NDA, compares TEAEs possibly associated with PAA toxicity or hyperammonemia in patients older than 6 years. In each category there are slightly more TEAEs of interest in the HPN-100 group than the NaPBA group, but the overall differences are slight and the TEAEs non-specific.

Table 28 TEAE in Short and Long Term Studies

System Organ Class Preferred Term ^c	Number (%) of Patients		
	Short-Term Controlled Studies ^a		Long-Term Open-Label Studies ^b
	NaPBA (N = 70)	HPN-100 (N = 65)	HPN-100 (N = 77)
Any related TEAE ^d	22 (31.4)	27 (41.5)	41 (53.2)
Gastrointestinal disorders	14 (20.0)	18 (27.7)	23 (29.9)
Diarrhoea	2 (2.9)	7 (10.8)	4 (5.2)
Flatulence	1 (1.4)	7 (10.8)	3 (3.9)
Nervous system disorders	5 (7.1)	7 (10.8)	7 (9.1)
Headache	2 (2.9)	7 (10.8)	3 (3.9)

[Ref: ISS, Table 2.7.4-16, p.43]

As an additional analysis the sponsor identified the MedRA term that was closest to the terms used to describe the adverse events in the Oncology patients and searched the AE profile for Ravicti using these updated terminologies. Adverse events seen in short-term and long-term Ravicti trials that corresponded to adverse events seen by Thibault are shown in the following two tables. In short-term studies no AEs similar to those described by Thibault were seen in pediatric patients, and mostly Grade 1 events were seen in adults. In addition, no major differences are seen between the two drugs. In the long-term studies no pediatric AE's were of a grade 3 level. Grade 2 headache was seen in two pediatric patients, and lightheadedness and headache were the most frequent grade 1 event, seen mostly in adults.

Table 29 Toxicities Reported to be Associated with PAA Reported during NDA2-3284 Short-Term Trials

Term Based on Thibault 1994/1995 Publication	NaPBA				HPN-100			
	Grade 1 (Mild)		Grade 2 (Moderate)		Grade 1 (Mild)		Grade 2 (Moderate)	
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric
Neurologic								
Somnolence	0	0	0	0	1 (1.9)	0	0	0
Fatigue	2 (3.4)	0	1 (1.7)	0	2 (3.7)	0	1 (1.9)	0
Headache	3 (5.1)	0	1 (1.7)	0	6 (11.1)	0	1 (1.9)	0
Lightheadedness ^a	5 (8.5)	0	0	0	0	0	0	0
Dysgeusia	2 (3.4)	0	0	0	0	0	0	0
Hypoacusis	0	0	0	0	0	0	0	0
Disorientation ^b	0	0	0	0	0	0	0	0
Exacerbation of neuropathy ^c	0	0	0	0	0	0	0	0
Impaired memory	0	0	0	0	0	0	0	0

[Ref: Summary Clinical Safety, Table 2.7.4-37, p.97.]

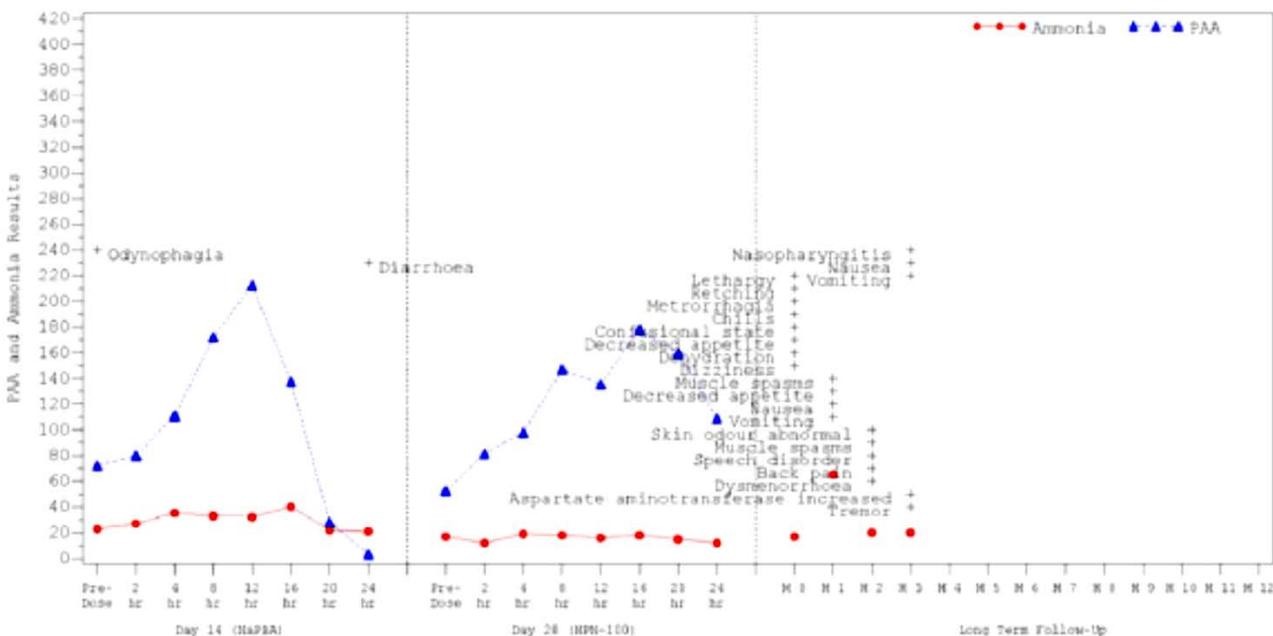
Table 30 Toxicities Reported to be Associated with PAA Reported during NDA203284 Long-Term Studies

Term Based on Thibault 1994/1995 Publication	Grade 1 (Mild)		Grade 2 (Moderate)		Grade 3 (Severe)		ALL
	Adult	Pediatric	Adult	Pediatric	Adult	Pediatric	
Neurologic							
Somnolence	1 (2.0)	0	0	0	0	0	1 (1.3)
Fatigue	4 (7.8)	2 (7.7)	2 (3.9)	0	0	0	8 (10.4)
Headache	7 (13.7)	2 (7.7)	1 (2.0)	2 (7.7)	0	0	12 (15.6)
Lightheadedness ^a	6 (11.8)	1 (3.8)	1 (2.0)	0	0	0	9 (11.7)
Dysgeusia	0	0	1 (2.0)	0	0	0	1 (1.3)
Hypoacusis	0	0	1 (2.0)	0	0	0	1 (1.3)
Disorientation ^b	0	0	1 (2.0)	0	0	0	1 (1.3)
Exacerbation of Neuropathy ^c	1 (2.0)	0	0	0	1 (2.0)	0	2 (2.6)
Impaired memory	0	0	0	0	0	0	0

[Ref: Summary Clinical Safety, Table 2.7.4-38]

The following four figures associate PAA and ammonia levels with adverse events. In Figure 13, at the time of the highest PAA level (212 µg/mL), while at steady state on NaPBA, the patient experienced the AEs ofodynophagia and diarrhea. Her ammonia level ranged from 12 to 19. At steady state for Ravicti she did not have an adverse event. She then enrolled in the long-term safety study from which she was withdrawn for multiple TEAEs after 107 days. Her highest ammonia level was at month 1 (65µmol/L) and was associated with nausea, vomiting, decreased appetite, and muscle spasms. No PAA levels were available, so an assessment of the relationship of PAA to TEAEs could not be made.

Figure 13 Adult with Highest PAA value and TEAEs during short and long term treatment



[Ref: Summary Clinical Safety, Figure 2.7.4-4, p.102]

Patient 20-7639 (shown below in Figure 14) had the highest PAA (394 µg/mL) recorded in an adult UCD patient during long-term treatment with HPN-100. She had three PAA levels in long-term follow-up studies, and serial PAA levels in short-term trial HPN-100-006. No PAA levels in short-term studies was higher than 60. She experienced one episode of hyperammonemia that was associated with gastroenteritis, and an event of hyperammonemia (red star).

Figure 15 shows the profile of pediatric patient 05-5052, enrolled in HPN-100-005 cross-over and safety-extension. As the figure shows, the patient had no AEs reported in short term studies even with a PAA level of 240. In the long-term study adverse events were associated with an upper respiratory infection.

Finally Figure 16 shows one patient from long-term safety study HPN-100-007 with an elevated PAA level but no associated adverse events.

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Figure 14 Adult UCD patient with highest PAA during Short and Long-term treatment with HPN-100

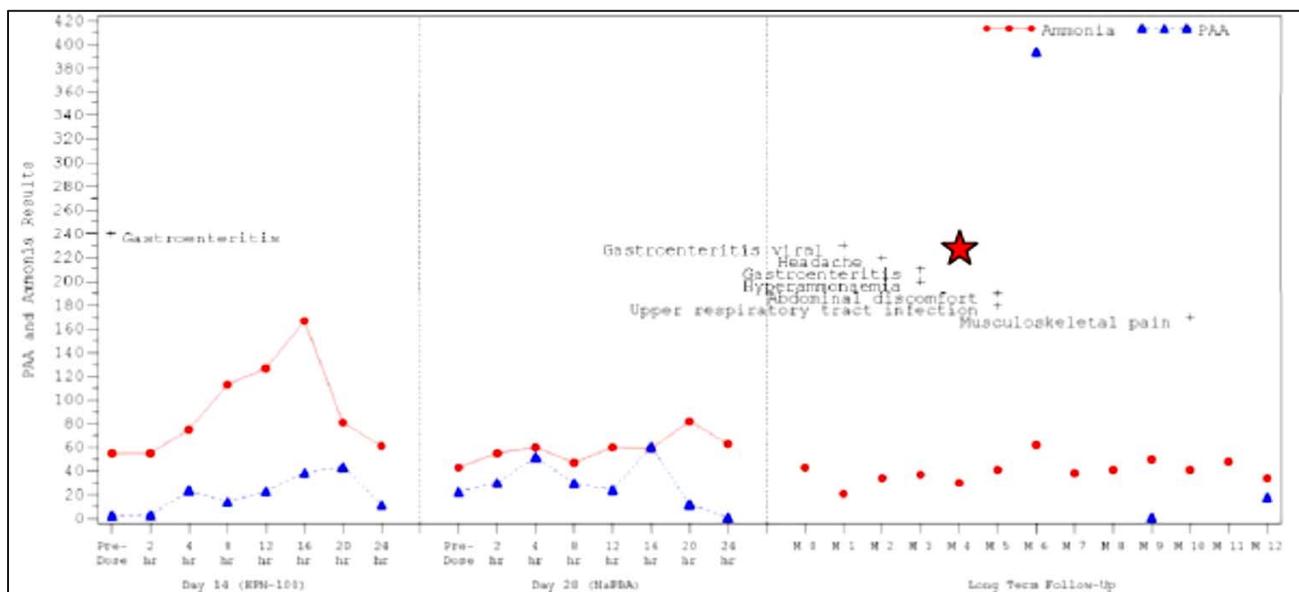
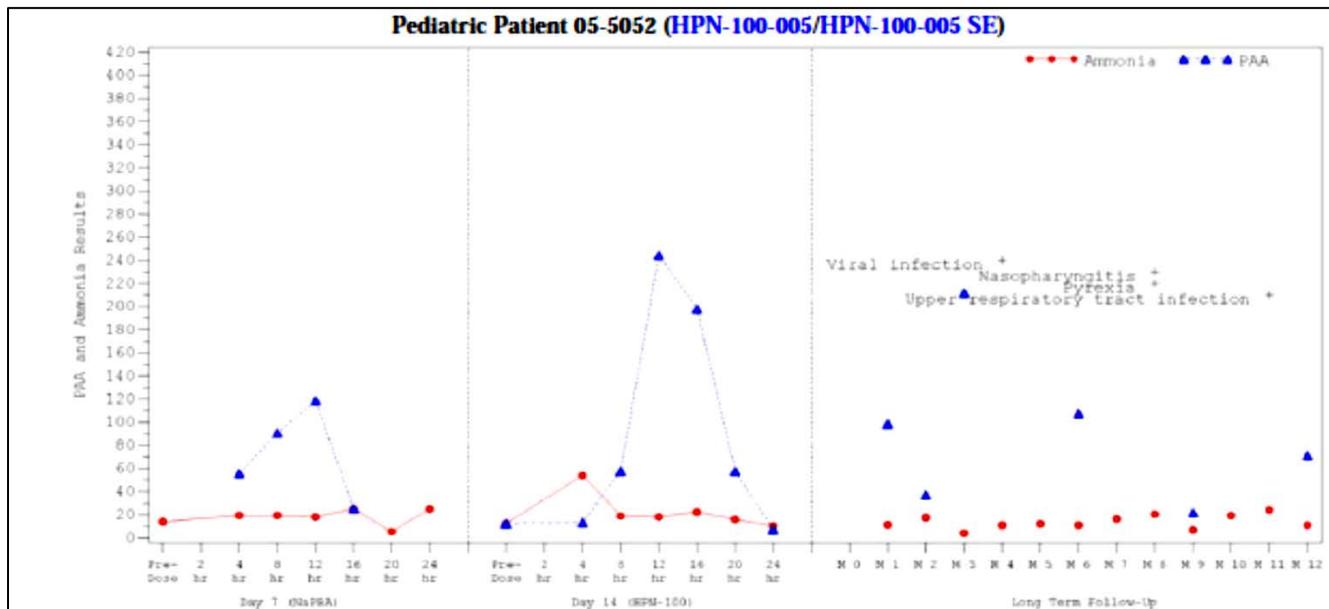
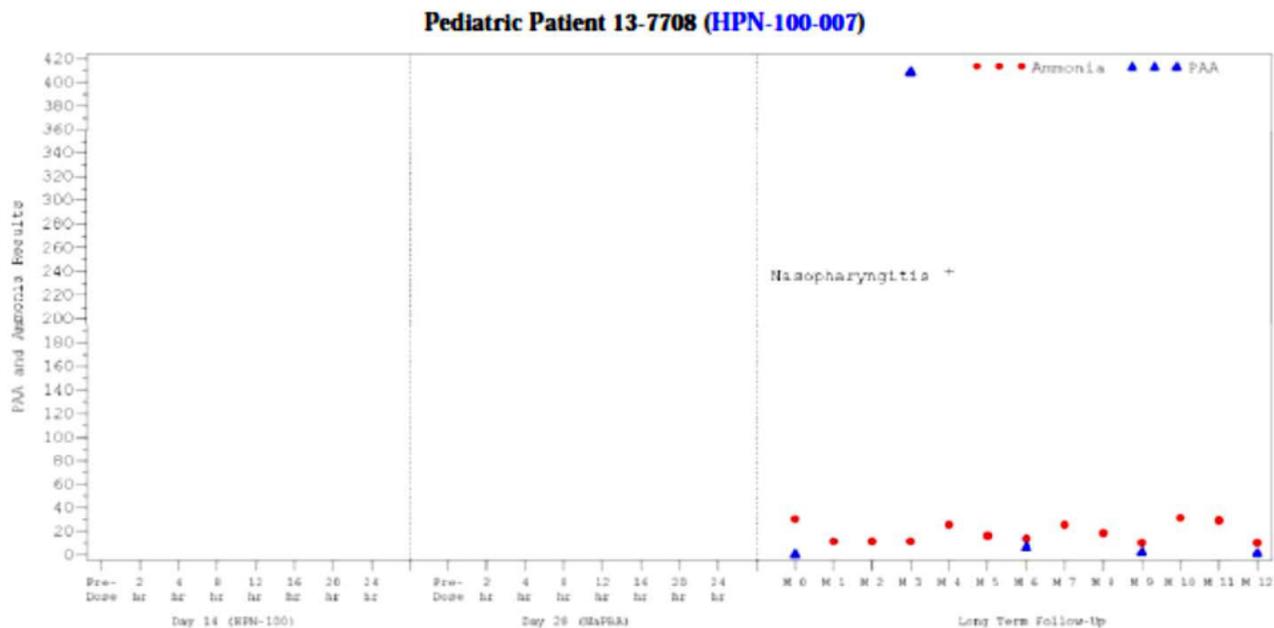


Figure 15 Pediatric UCD patients with highest PAA with Ammonia and TEAEs



[Ref: Summary of Clinical Safety, Figure 2.7.4-5. p103.]

Figure 16 Pediatric UCD Patient with PAA, Ammonia and TEAEs



[Ref: Summary of Clinical Safety, Figure 2.7.4-5, p.103]

Reviewer's Comment:

The preceding four figures illustrate a lack of association between adverse events and PAA levels. However as noted above PAA levels were obtained at less frequent intervals in long-term studies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common TEAE were defined as TEAEs occurring in $\geq 10\%$ patients or subjects. Not surprisingly the incidence of common TEAEs was higher in the long-term open-label studies than in the short-term controlled studies. However as the duration of treatment increased, the percentage of common adverse events decreased. For example during months 0 to <3 seventy-seven percent of patients had at least one TEAE, as compared with 69% in the time period 9 to <12 months. As noted earlier in this review, the only study that directly compared safety and efficacy between Buphenyl and Ravicti was HPN-100-006 in which patients had a two week period on each drug. In that study the number of adverse events between the two groups was similar. Approximately nine percent of patients on NaPBA had dizziness, compared to none on Buphenyl. There were slightly more headaches on Ravicti compared to Buphenyl. There was more flatulence and diarrhea on Ravicti than Buphenyl. Common adverse events from HPN-100-006 are shown in Table 31.

Table 31 TEAE in ≥ 2 patient HPN-100-006

System Organ Class Preferred Term	Number of Patients, n (%)	
	NaPBA (N = 45)	HPN-100 (N = 44)
Patients Reporting Any TEAE	23 (51.1)	27 (61.4)
Gastrointestinal Disorders	13 (28.9)	16 (36.4)
Abdominal discomfort	3 (6.7)	0
Abdominal pain	2 (4.4)	3 (6.8)
Diarrhoea	3 (6.7)	7 (15.9)
Dyspepsia	3 (6.7)	2 (4.5)
Flatulence	1 (2.2)	6 (13.6)
Nausea	3 (6.7)	1 (2.3)
Oral discomfort	2 (4.4)	0
Vomiting	2 (4.4)	3 (6.8)
Nervous System Disorders	7 (15.6)	7 (15.9)
Dizziness	4 (8.9)	0
Headache	4 (8.9)	6 (13.6)
General Disorders and Administration Site Conditions	2 (4.4)	5 (11.4)
Fatigue	1 (2.2)	3 (6.8)
Metabolism and Nutrition Disorders	4 (8.9)	3 (6.8)
Decreased appetite	2 (4.4)	3 (6.8)
Increased appetite	2 (4.4)	0
Investigations	2 (4.4)	3 (6.8)
Ammonia increased	1 (2.2)	2 (4.5)
Psychiatric Disorders	2 (4.4)	1 (2.3)
Food aversion	2 (4.4)	1 (2.3)
Skin and Subcutaneous Tissue Disorders	2 (4.4)	2 (4.5)
Dermatitis contact	0	2 (4.5)

[Ref: CSR HPN-100-006, Table 34, p.94.]

In long-term studies patients were followed for 12 months. Consequently the number of common TEAEs would be expected to be greater than in the short-term studies. The only TEAEs seen in Ravicti patients in long-term, but not short-term studies were dizziness and hyperammonemia. Events of hyperammonemia occurred in UCD patients in the 12 months prior to starting the Ravicti trials and are indicative of how difficult this disease is to manage.

Table 32 Common TEAS in UCD patients short and long term studies

System Organ Class Preferred Term ^c	Number (%) of Patients		
	Short-Term Controlled Studies ^a		Long-Term Open-Label Studies ^b
	NaPBA (N = 70)	HPN-100 (N = 65)	HPN-100 (N = 77)
Any TEAE	33 (47.1)	37 (56.9)	75 (97.4)
Gastrointestinal disorders	18 (25.7)	21 (32.3)	42 (54.5)
Vomiting	3 (4.3)	4 (6.2)	23 (29.9)
Nausea	7 (10.0)	1 (1.5)	14 (18.2)
Diarhoea	4 (5.7)	7 (10.8)	12 (15.6)
Flatulence	1 (1.4)	7 (10.8)	3 (3.9)
Nervous system disorders	11 (15.7)	8 (12.3)	30 (39.0)
Headache	4 (5.7)	7 (10.8)	12 (15.6)
Dizziness	5 (7.1)	0	9 (11.7)
Metabolism and nutrition disorders	7 (10.0)	6 (9.2)	25 (32.5)
Hyperammonemia	2 (2.9)	0	12 (15.6)
Decreased appetite	3 (4.3)	3 (4.6)	10 (13.0)
General disorders and administration site conditions	3 (4.3)	6 (9.2)	20 (26.0)
Fatigue	1 (1.4)	3 (4.6)	8 (10.4)
Infections and infestations	3 (4.3)	5 (7.7)	51 (66.2)
Upper respiratory tract infection	0	2 (3.1)	23 (29.9)
Nasopharyngitis	0	1 (1.5)	13 (16.9)
Respiratory, thoracic, and mediastinal disorders	0	3 (4.6)	22 (28.6)
Cough	0	2 (3.1)	10 (13.0)
Oropharyngeal pain	0	2 (3.1)	8 (10.4)

[Ref: ISS, Table 2.7.4-15, p.42]

Reviewer's Comment:

There were 57% TEAEs in the HPN-100 treated patients compared to 47% in those receiving NaPBA. There were more GI-related TEAEs in patients taking HPN-100. This may be explained by the fact that some patients were switched from G-tube administration to oral administration. There were 16% nervous system disorders in Buphenyl patients compared to 12% in patients receiving Ravicti. The major difference was in the TEAE of dizziness, seen in 7.1% of patients receiving Buphenyl, compared to none in patients receiving Ravicti.

7.4.2 Laboratory Findings

Four laboratory parameters are discussed: liver function, hematology, chemistry, and coagulation studies.

Liver Function:

There were no significant changes in biochemical liver tests in short-term controlled trials in UCD patients. In long-term open label studies 5% of laboratory AEs was for

elevations of ALT, 6% elevations of AST, and 1.3% elevations in bilirubin. Table 33 shows changes from baseline to month 12 in long-term open-label studies.

Table 33 Change from Baseline and Shifts in Liver Function Tests in Long-Term Open-Label Studies HPN-100

Parameter	Change from Baseline		Shifts from Baseline		Reported as an AE
	n	Mean	High→Normal n/N (%)	Normal→High n/N (%)	n/N (%)
ALT (IU/L)					4/77 (5.2)
Month 3	73	3.3	4/8 (50.0)	3/61 (4.9)	
Month 6	69	5.2	5/8 (62.5)	4/59 (6.8)	
Month 9	67	4.5	5/8 (62.5)	3/57 (5.3)	
Month 12	68	6.8	4/8 (50.0)	5/58 (8.6)	
AST (IU/L)					5/77 (6.5)
Month 3	73	0.3	10/13 (76.9)	6/57 (10.5)	
Month 6	69	0.7	9/13 (69.2)	8/54 (14.8)	
Month 9	67	0.3	8/13 (61.5)	5/51 (9.8)	
Month 12	68	3.3	9/12 (75.0)	5/52 (9.6)	
Alkaline Phosphatase (IU/L)					0/77
Month 3	73	-4.9	0/4 (0.0)	1/64 (1.6)	
Month 6	69	-4.0	0/4 (0.0)	2/60 (3.3)	
Month 9	67	-4.1	0/4 (0.0)	1/59 (1.7)	
Month 12	68	-2.7	0/4 (0.0)	2/60 (3.3)	
Bilirubin (µmol/L)					1/77 (1.3)
Month 3	73	-0.434	1/2 (50.0)	1/66 (1.5)	
Month 6	69	-0.188	0/1 (0.0)	2/63 (3.2)	
Month 9	67	-0.143	2/3 (66.7)	0/59	
Month 12	68	0.574	2/3 (66.7)	2/60 (3.3)	
			Normal→Low n/N (%)	Low→Normal n/N (%)	
Albumin (g/L)					2/77 (2.6)
Month 3	73	2.4	1/69 (1.4)	4/4 (100.0)	
Month 6	69	2.1	1/66 (1.5)	2/3 (66.7)	
Month 9	67	1.4	0/65	2/2 (100.0)	
Month 12	66	1.8	2/64 (3.1)	0/2	

[Ref: Summary Clinical Safety, Table 2.7.4-49, p.122.]

One patient had an increase in bilirubin from baseline normal of 10.26 µmol/L to 13.68 at month 4, and 17.1 at month 12. The increase at month 4 coincided with starting levetiracetam (Keppra®). The drug labeling for Keppra lists increase in liver tests as a post-marketing AE, and given the temporal association between starting the drug and seeing an increase in liver tests, this is the likely cause. Another patient in long-term studies had increases in ALT and AST which appeared to be related to concomitant use of risperidone and methylphenidate. The AST and ALT were normal or near normal at the end of the study.

Hematology:

In short-term studies differences between HPN-100 and NaPBA in hematocrit were observed. Thirty-two% (20/62) and 19.4% (12/62) of patients treated with HPN-100 and NaPBA had low values at steady state. In long term studies (seen below in Table 34) few shifts from normal at baseline were noted.

Table 34 Summary of Changes from Baseline and Shifts in Hematology Parameters HPN-100 Open-Label Studies

	Change from Baseline		Shifts from Normal at Baseline		Reported as an AE
	n	Mean	Normal→Low	Normal→High	
			n/N (%)	n/N (%)	n/N (%)
Platelets (10⁹/L)					2/77 (1.3)
Month 3	73	5.6	2/67 (3.0)	1/67 (1.5)	
Month 6	69	4.8	4/64 (6.3)	2/64 (3.1)	
Month 9	66	6.4	3/60 (5.0)	1/60 (1.7)	
Month 12	68	8.0	2/62 (3.2)	1/62 (1.6)	
Hemoglobin (g/L)					1/77 (1.3)
Month 3	73	2.7	5/54 (9.3)	3/54 (5.6)	
Month 6	70	2.6	2/50 (4.0)	4/50 (8.0)	
Month 9	66	2.7	4/48 (8.3)	2/48 (4.2)	
Month 12	68	3.7	2/49 (4.1)	3/49 (6.1)	
Leukocytes (10⁹/L)					2/77 (2.6)
Month 3	73	-0.019	3/63 (4.8)	1/63 (1.6)	
Month 6	70	0.107	6/61 (9.8)	0/61	
Month 9	66	0.079	5/57 (8.8)	3/57 (5.3)	
Month 12	68	0.157	3/60 (5.0)	2/60 (3.3)	

[Ref: Summary of Clinical Safety, Table 2.7.4-43]

Chemistry:

No significant changes in chemistry labs were seen in short-term studies. Five patients developed an abnormal clinical chemistry during long-term treatment with HPN-100 that was reported as an AE; 01-7643 (decreased blood bicarbonate), 06-7705 (hyperglycemia), 07-5071 (decreased blood potassium), and 17-7609 (increased blood potassium), and 17-7610 (increased blood urea nitrogen).

None of these AE resulted in discontinuation from the study and the exact etiology of the laboratory AE was not clear. In the case of decreased serum bicarbonate, recent vomiting and dehydration may have been the cause. The decreased albumin was possibly due to poor nutrition and the hyperglycemia multifactorial. Overall, laboratory shifts in long term studies were minimal.

Table 35 Shift Tables Chemistry HPN-100 Long-Term Studies

Parameter	Change from Baseline		Shifts from Normal at Baseline		Reported as AE n/N (%)
	n	Mean	Normal→Low n/N (%)	Normal→High n/N (%)	
BUN (mmol/L)					1/77 (1.3)
Month 3	72	-0.058	13/47 (27.7)	0/47	
Month 6	69	-0.099	12/45 (26.7)	0/45	
Month 9	66	-0.052	10/43 (23.3)	0/43	
Month 12	67	-0.182	14/44 (31.8)	0/44	
Sodium (mmol/L)					0/77
Month 3	73	-0.3	1/71 (1.4)	1/71 (1.4)	
Month 6	70	-0.1	1/68 (1.5)	1/68 (1.5)	
Month 9	67	0.1	0/66	1/66 (1.5)	
Month 12	68	0.0	0/67	2/67 (3.0)	
Potassium (mmol/L)					2/77 (2.6)
Month 3	73	-0.02	1/70 (1.4)	1/70 (1.4)	
Month 6	70	0.07	0/67	2/67 (3.0)	
Month 9	67	-0.03	1/64 (1.6)	0/64	
Month 12	68	0.12	1/65 (1.5)	5/65 (7.7)	
Chloride (mmol/L)					0/77
Month 3	73	-0.7	0/58	6/58 (10.3)	
Month 6	70	-0.4	0/56	4/56 (7.1)	
Month 9	67	-0.1	0/54	6/54 (11.1)	
Month 12	68	-0.2	0/56	7/56 (12.5)	
Bicarbonate (mmol/L)					1/77 (1.3)
Month 3	68	-1.50	9/59 (15.3)	2/59 (3.4)	
Month 6	65	-1.18	11/57 (19.3)	3/57 (5.3)	
Month 9	62	-0.75	7/56 (12.5)	2/56 (3.6)	
Month 12	64	-0.93	5/57 (8.7)	3/57 (5.3)	
Creatinine (µmol/L)					0/77
Month 3	73	0.448	7/58 (12.1)	2/58 (3.4)	
Month 6	70	-0.376	6/57 (10.5)	1/57 (1.8)	
Month 9	67	-1.846	10/53 (18.9)	1/53 (1.9)	
Month 12	68	-0.965	7/55 (12.7)	1/55 (1.8)	
Glucose (mmol/L)					1/77 (1.3)
Month 3	73	-0.060	1/62 (1.6)	1/62 (1.6)	
Month 6	70	0.100	1/61 (1.6)	2/61 (3.3)	
Month 9	66	0.111	1/56 (1.8)	1/56 (1.8)	
Month 12	68	-0.014	0/57	1/57	

[Ref: Summary Clinical Safety, Table 2.7.4-45, p.118.]

Coagulation Studies:

One patient had reported as an AE an increase in prothrombin time. The prothrombin time was 12.6 sec on day 28, and increased to 16.9 sec at month 12. The cause of the increased PT was not given.

Table 36 Shifts from baseline Coagulation Parameters Long-Term

Parameter	Change from Baseline		Shifts from Baseline		Reported as an AE
	n	Mean	High→Normal n/N (%)	Normal→High n/N (%)	n/N (%)
Prothrombin time (s)					1/77
Month 3	58	0.010	5/8 (62.5)	5/44 (11.4)	
Month 6	57	0.011	2/8 (25.0)	2/44 (4.5)	
Month 9	53	-0.017	1/5 (20.0)	4/43 (9.3)	
Month 12	55	-0.111	3/8 (37.5)	4/42 (9.5)	
Prothrombin INR					0/77
Month 3	68	-0.005	2/3 (66.7)	2/32 (6.3)	
Month 6	67	-0.008	2/3 (66.7)	1/30 (3.3)	
Month 9	64	-0.007	1/1 (100.0)	2/30 (6.7)	
Month 12	66	-0.007	1/3 (33.5%)	0/31	

[Ref: Summary Clinical Safety, Table 2.7.4-47, p. 119.]

Reviewer's Comment:

None of these laboratory AEs raise new concerns about Ravicti. In most cases the cause was due to concomitant medications, diet or co-morbid conditions.

7.4.3 Vital Signs

There were no significant changes in blood pressure, heart rate, respiratory rate or temperature during short-term controlled studies or long-term open-label studies.

7.4.4 Electrocardiograms (ECGs)

There were no changes from baseline in ECGs in short or long term studies suggestive of a drug effect.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT/QTc Study in Healthy Volunteers: HPN-100-010:

Eighty-six healthy subjects were randomized to receive 4 treatment regimens (placebo, moxifloxacin, HPN-100 at a therapeutic dose, and HPN-100 at a supratherapeutic dose). Each treatment period was for 3 days with a 4-day minimum washout period. The therapeutic dose was 4 mL TID (13.2 g/day), which is similar to the average dose received by UCD patients in short-term and long term studies (13.21 g/day and 12.77g/day respectively). Although the study was negative for QT prolongation by HPN-100 up to 19.8 g/d, the sensitivity of the study was not adequately established. The moxifloxacin induced QT prolongation at 0.5 hours post-dose was earlier than expected, and there was no return to a placebo/baseline-range reading. These findings were unexpected given the PK profile of moxifloxacin (Tmax 1 to 4 hours).

Reviewer's Comment:

Ravicti did not show QT prolongation effects. However because moxifloxacin showed QT prolongation earlier than expected, and did not return to baseline, the overall results of the tQT study may be unreliable and should be repeated. No tQT study was performed for Buphenyl.

7.4.6 Immunogenicity

Because Ravicti is a small, non-biologic molecule, immunogenicity should not be an issue.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See individual adverse events.

7.5.2 Time Dependency for Adverse Events

See individual adverse events.

7.5.3 Drug-Demographic Interactions

In short-term studies there were no clinically significant differences in TEAEs, TESAEs, and TESAEs leading to discontinuation between the two drugs with respect to age, sex, race or UCD subtype. There were more TEAEs in the HPN-100 arm in the youngest age group because patients were switched to Ravicti on day 2. In the 6 to 11 year age group there were four TEAEs in the Ravicti group compared to one in the Buphenyl. Among the TEAEs in the HPN-100 group were two events of upper abdominal pain, and one event each of vomiting, ear infection, upper respiratory infection, and dermatitis. In the Buphenyl group there was one event of lymphadenopathy and one event of cardiac murmur (Table 37).

Table 37 TEAE & TESAE Short-Term Trials

	Total TEAS by Number (%) Patients					
	NaPBA			HPN-100		
	TEAE	TESAE	TEAE led to D/C	TEAE	TESAE	TEAE led to D/C
Age						
<6	0	0	0	6 (40)	0	0
≥6 -11	1 (14)	0	0	4 (57)	0	0
≥12-17	1 (25)	0	0	0	0	0
≥18	31 (52)	2 (3)	2(3)	33 (61)	1(2)	0
Sex						
Male	9(45)	1 (5)	1 (5)	9 (50)	1 (6)	0
Female	24 (48)	1 (2)	2 (2)	28 (60)	0	0
Race						
White	23(43)	2(4)	1 (2)	31 (62)	1 (2)	0
Non-white	10 (59)	0	2 (6)	6 (40)	0	0
UCD type						
OTC	27 (45)	8 (40)	0	1 (2)	1 (2)	0
Non-OTC	6 (67)	25 (50)	2 (4)	0	0	0

[Red: adapted from Summary of Clinical Safety, Table 2.7.4-54, p.140]

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Because of the rapid degradation of Ravicti, drug-drug interactions are not expected.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies have been done.

7.6.2 Human Reproduction and Pregnancy Data

The effect of Ravicti on human reproduction and pregnancy is unknown.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies have been of adequate duration to assess the effects of Ravicti on growth parameters. However the sponsor plans a Phase 4 study which will be a long-term registry of Patients with Urea Cycle Disorders. The proposed study will be of 10 years duration, and will monitor control of blood ammonia, SAEs, pregnancy outcomes, neuropsychological testing, growth and development, and UCD medication discontinuation or change in medication.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with over dosage in the clinical trials for HPN-100. The labeling for HPN-100 will contain the same recommendations for supportive measures as for NaPBA. In the event of overdose the drug should be discontinued, supportive measures instituted, and dialysis as needed. Drug abuse is not expected, and no case of drug abuse has been reported during the clinical trials.

The sponsor did not conduct studies to evaluate rebound effects. Treatment with nitrogen scavenging drugs cannot be withdrawn.

7.7 Additional Submissions / Safety Issues

No additional issues are presented in this section.

8 Postmarket Experience

There is no postmarket experience for Ravicti because it is not approved at the time of the review.

9 Appendices

None.

9.1 *Literature Review/References*

See footnotes.

9.2 *Labeling Recommendations*

Labeling recommendations are pending, and will be discussed separately.

9.3 *Advisory Committee Meeting*

Not applicable.

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/s/

NANCY C SNOW
12/04/2012

MELANIE J BLANK
12/06/2012

CLINICAL FILING CHECKLIST FOR NDA 203284

NDA Number: 203284 Applicant: Hyperion Stamp Date: December 23, 2011

Drug Name: Ravicti (glycerol phenylbutyrate) Liquid NDA Type:

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Narrative portion is in Module 2.7, with tables, figures, and datasets in Module 5.3.5.3.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Narrative portion is in Module 2.7, with tables, figures, and datasets in Module 5.3.5.3.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5 Section 6. REMS proposed to (b) (4)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: UP 1204-003: Open-Label, Switch-Over, Dose-Escalation Study to evaluate the safety, tolerability,	X			Ravicti PBA dose was made equivalent to FDA-approved NaPBA (Buphenyl) dosing

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CLINICAL FILING CHECKLIST FOR NDA 203284

	Content Parameter	Yes	No	NA	Comment
					of safety based on NaPBA (Buphenyl).
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			Exposure is adequate for this rare disease: 246 overall (includes healthy volunteers), 91 UCD patients overall, 3 UCD patients for 6 months 69 UCD patients for one year
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			PAA levels and neurological adverse events
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			HPN-100-012 (UCD patients < 6 years of age) is currently enrolling and not included in this NDA submission.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Ravicti was granted orphan designation on April 27, 2009
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		All clinical sites were US, except for one in Canada and one in the

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA 203284

	Content Parameter	Yes	No	NA	Comment
					Ukraine.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following components of the application are missing and must be submitted:

1. *A rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.*

Tamara Johnson, MD, MS
 Reviewing Medical Officer

January 26, 2012

Date

Lynne Yao, MD
 Clinical Team Leader

January 30, 2012

Date

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

/s/

TAMARA N JOHNSON
02/08/2012

LYNNE P YAO
02/08/2012