CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	203284
Applicant Name	Hyperion Therapeutics, Inc.
Date of Submission	December 23, 2011
PDUFA Goal Date	January 23, 2013 Action Date: February 1, 2013
Proprietary Name / Established (USAN) Name	Ravicti/ glycerol phenylbutyrate
Dosage Forms / Strength	Liquid for oral administration 1.1 g of glycerol phenylbutyrate (GPB) in 1 ml of Ravicti® (equivalent to 1.02 g phenylbutyrate)
Proposed Indication(s)	Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders (UCD) involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH) deficiency.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nancy Snow, DO/Melanie Blank, MD
Statistical Review	Behrang Vali, MS/Mike Welch, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/David Joseph, PhD
CMC Review	Hamid Shafiei, PhD/Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Insook Kim, PhD/Sue Chih Lee, PhD
DPDP/OPDP	Kathleen Klemm
DSI	K. Malek, MD/Susan Leibenhaut, MD/Susan Thompson, MD
CDTL Review	Melanie Blank, MD
OSE/DMEPA	Lubna Merchant, PharmD, MS/Kellie Taylor, PharmD, MPH/Carol Holquist, RPh
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PMHS	Alyson Karesh, MD/Hari Cheryl Sachs, MD/ Jeanine Best/Melissa Tassinari, PhD/Lynne Yao, MD
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SEALD	Eric Brodsky, MD/Jeanne Delasko/Laurie Burke
Interdisciplinary Review Team for QT Studies	J. Zhang/Q. Dang/D. Marathe/N. Mehrotra/M. Fiszman/N.Stockbridge

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

Division Director Summary Review

1. Introduction

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

> "Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders (UCD) involving deficiencies of the following enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) or arginase (ARG) as well as the mitochondrial transporter ornithine translocase (HHH) deficiency."

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

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

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

In keeping with multiple interactions with the Division during the clinical development of Ravicti, including a SPA agreement, the safety and efficacy data submitted in support of the NDA hinge on a trial conducted to establish noninferiority of Ravicti to the approved Buphenyl (sodium phenylbutyrate) product in control of venous ammonia level, based on 24-hour AUC of ammonia (AUC_{NH3}). This trial (Study 006), which was conducted in adult patients with UCD, was essentially designed to demonstrate bioequivalence of the two products for the PD marker, AUC_{NH3}, specifically focusing on the upper bound of the confidence interval, i.e., the AUC_{NH3} ratio of the geometric means for Ravicti/Buphenyl must not exceed 1.25. Ammonia levels were considered an acceptable endpoint to establish efficacy, since high serum ammonia levels are known to cause serious morbidity and mortality in patients with urea cycle disorders (UCD). Ammonia was utilized as an endpoint to support the 2010 regular approval of Carbaglu for the UCD, N-acetylglutamate synthase (NAGS) deficiency.

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

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

naïve patients and the lack of specific instructions for initiating therapy in the Buphenyl label (beyond providing a range), was a significant review issue that impacted labeling decisions. The investigators for the Ravicti trials have stated in a publication in Molecular Genetics and Metabolism [Mokhtarani M, et al. 107 (2012) 308-314], "Although sodium phenylbutyrate has been used for the treatment of UCDs since at least 1979, comparatively little information is available to guide physicians regarding its optimal dosing."

2) There were limitations to the strength of evidence provided in the NDA to support inclusion of information proposed by the applicant in the product label on how to modify dose based on various biomarkers, aside from venous ammonia levels.

3) Ravicti is a pre-pro-drug. The drug must be released from the glycerol backbone to enable systemic absorption of therapeutic levels of phenylbutyrate (which is subsequently converted to the PAA molecule that binds glutamine to clear nitrogen). Because young infants, less than 2 months of age, are known to have immature pancreatic function, there is a scientifically known reason to have concern that infants less than 2 months of age will not absorb therapeutic levels of phenylbutyrate, due to low levels of pancreatic lipases. This is not an issue for the currently marketed sodium phenylbutyrate product. Because ineffective treatment of blood ammonia levels in a young infant could result in devastating outcomes, there was substantial concern that without a contraindication there would be substitution errors of Ravicti for Buphenyl in this age group, since both contain phenylbutyrate. This concern resulted in a Contraindication for use in this age group.

4) Inadequate data were submitted to establish a safe dose in children between the age of 2 months and 2 years. There were only 4 children studied in this age range and the data collected were inadequate for Clinical Pharmacology reviewers to determine safe dose recommendations. The Division had strongly encourage the sponsor during the clinical development to obtain adequate clinical data to cover all relevant age groups, recognizing that if Ravicti was in fact more palatable, it would be exceedingly important to have sufficient data to support labeling a safe and effective dose of Ravicti across all pediatric age groups. This gap will be addressed with a PMR under FDAAA, in light of the safety issue related to PAA. PREA does not apply since the applicant's product has orphan designation for UCDs. The product label will state that the safety and efficacy have not been established in this age range (2 months to less than 2 years).

5) The reviewers considered whether a comprehensive list of UCD subtypes (as proposed by the applicant) enrolled in the various trials submitted to the NDA should be included in the labeled indication for Ravicti, whether or not the number enrolled with a specific subtype was quite small. The Buphenyl label precedent was considered, which on first glance appears relatively limited compared to the applicant's proposal; however, the additional text regarding neonatal onset and late onset in that indication seems broad and more encompassing. Ultimately, the reviewers considered the variability in the clinical presentations of the phenotypes (both among specific UCD subtypes and within specific subtypes), how the drug functions biochemically to reduce nitrogen, and how this product is clinically used as an adjunct, and determined that more general language was appropriate for the Indication section of the label. However, in keeping with the Buphenyl indication,

the reviewers determined that the Ravicti indication should communicate that the product should be reserved for use only in patients who need it to manage serum ammonia. The risk of carcinogenesis and the risk of neurotoxicity from PAA cannot be justified if a patient's nitrogen can be managed by other standard measures. Patients with UCDs are managed by specialists in treatment of these diseases and the reviewers were confident that these limitations outlined in the indication would be adhered to without additional measures to assure safe use because the specialists who care for these patients are aware of these issues and currently practice within guidelines.

6) The reviewers further considered the risk/benefit implications of the nonclinical carcinogenicity study results, and how this should be managed in product labeling. Ultimately, this (and the neurotoxicity associated with PAA, the active metabolite of Ravicti) impacted the Nursing Mothers section of the label and resulted in a PMR to obtain levels of the drug and its metabolites in breast milk, since nursing infants (particularly those without a diagnosis of UCD) would not have the same risk/benefit ratio for exposure to Ravicti as patients with a UCD.

I will address these issues in the context of this review.

2. Background

The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals and consists of 6 enzymes: (*N*-acetyl-glutamate synthetase, carbamyl phosphate synthetase [CPS], ornithine transcarbamylase [OTC], argininosuccinate synthetase [AS], argininosuccinate lyase [AL], and arginase). Each turn of the cycle results in elimination of two nitrogens in the form of urea. (See Figure 1 below). Urea cycle disorders result from a deficiency of any of the enzymes involved in the urea cycle. These disorders are autosomal recessive diseases, with the exception of ornithine transcarbamylase deficiency, which is an X-linked disorder. As stated in the CDTL review, the prevalence of Urea cycle disorders in the US is estimated to be 1:8200, with an overall incidence of approximately 1 in 45,000 live births.

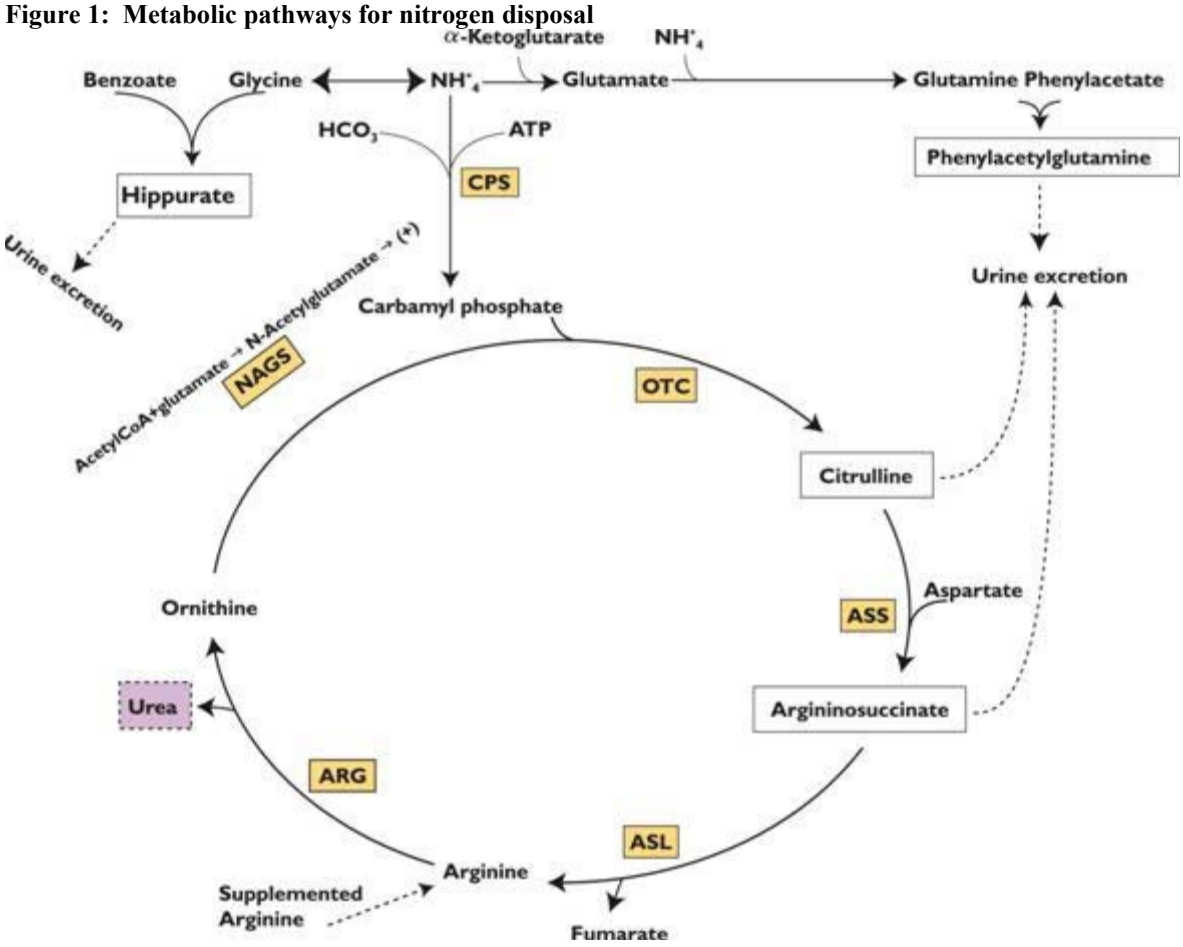
UCDs are characterized by hyperammonemia, encephalopathy, and respiratory alkalosis. Patients with UCDs are at high risk for neurologic deficits and death secondary to hyperammonemia. Patients may present with clinical manifestations across the lifespan, including as newborn/infants and in early childhood. The CDTL review provides a discussion of the variable phenotypic presentations. Partial enzyme deficiencies may present later in life, and depending on the level of function of the enzyme affected and the specific enzyme, patients may only require dietary management and nutritional supplements for chronic management of their disease.

Current treatments for UCDs include restriction of nitrogen load by a low protein diet, oral neomycin to decrease bacterial ammonia production, and the use of NH_3 scavengers. There are two nitrogen scavengers approved in the US for treatment of hyperammonemia in patients with UCDs: Buphenyl [(oral sodium phenylbutyrate (NaPBA)], Ammonul (intravenous mixture of sodium benzoate and sodium phenylacetate (NaPAA). Compounding pharmacies provide sodium phenylacetate and sodium benzoate for oral use. Carbaglu (carglumic acid), a specific

treatment for the UCD called NAGS deficiency, is a structural analogue of NAG, which is the essential allosteric activator of the enzyme CPS. Carbaglu does not function as a nitrogen scavenger, but instead serves to activate the key enzyme "at the top" of the urea cycle (see Figure below).

Ravicti contains three molecules of 4-phenylbutyric acid (PBA) bonded via ester linkages to a glycerol backbone. It is converted into one glycerol and three phenylbutyrate (PBA) molecules either in the gut or during trans-enteric transport, and is converted by β-oxidation into PAA, which binds to glutamine. The resulting conjugate, PAGN (phenylacetylglutamine, see Figure below), is excreted via kidney. Since glutamine contains two nitrogens, this results in elimination of two nitrogens from the body.

Figure 1: Metabolic pathways for nitrogen disposal



Adapted from: http://www.drugs.com/pro/ammonul.html (12-March-2009)

As discussed in the Introduction, one of the major review issues considered during product labeling was whether the indication should be limited to only those disorders in which there had been adequate characterization of safety and efficacy in the NDA trials. Ultimately, considering that the alternative pathway of nitrogen disposal that PAA provides, outside of the cycle, the review team determined that a general indication could be justified, as long as the indication clearly stated that the product was to be used only as an adjunct to other standard

interventions, such as diet, and that it should be used only if those other standard interventions were inadequate by themselves to manage the patient's nitrogen.

Regulatory background. Key goals for the interactions between FDA and the applicant during the clinical development of Ravicti included defining the appropriate endpoint for establishing efficacy and assuring that adequate numbers of children were studied to support defining a safe and effective dose across the full age range of patients who are affected by UCDs. I have summarized content from specific interactions between FDA and the applicant that impacted the content and review of the submitted NDA and/or labeling below.

Pre-IND Meeting December 12, 2005:

1) FDA told IND sponsor that because available pharmacokinetic data did not establish that Ravicti was bioequivalent to sodium phenylbutyrate, based on phenylbutyrate levels, PAA and PAGN levels, an efficacy trial would be required to support a marketing application.
2) FDA suggested that the primary efficacy objective for an efficacy trial should include AUC_{NH3} and 24-hour urinary excretion of glutamine-related compounds.

End of Phase 2 Meeting January 14, 2009:

1) FDA recommended that the primary efficacy objective for phase 3 trial(s) intended to support registration should be a co-primary of AUC_{NH3} and AUC of PAGN. FDA recommended that the sponsor consider a bioequivalence approach to analyses of the primary endpoint, and that the definition of success should also include that the AUC_{NH3} does not exceed 100 micromol/L.
2) The sponsor proposed (b) (4) The FDA recommended that the pediatric trial should be completed prior to initiating the proposed "pivotal" efficacy trial (Study 006), to inform assumptions used to power the trial. The FDA recommended that if the sponsor initiated Study 006 before the completion of Study 005, that children should be excluded from Study 006.
3) The FDA stated that adult efficacy data might be "extrapolatable" to the pediatric population; however, the dose and safety in children is not.
4) The FDA stated that the safety database for an NDA should include at least 35-40 patients who have been evaluated for at least 12 months on treatment.

SPA No Agreement Letter issued to sponsor on April 3, 2009:

1) Sponsor proposed that the primary efficacy endpoint of Study 006 would be (b) (4) would be evaluated as a secondary endpoint.
2) The FDA did not agree and stated that the primary endpoint should be AUC_{NH3}. AUC of blood PAGN and 24 hour urinary PAGN excretion should be a secondary endpoints. Other secondary endpoints of interest were number of hyperammonemic crises and severity of hyperammonemic crises.

Ravicti (glycerol phenylbutyrate) received Orphan Drug designation for maintenance of treatment of patients with deficiencies in enzymes of the urea cycle on April 27, 2009.

Meeting to discuss SPA No Agreement Letter on May 7, 2009:

1) Sponsor agreed to a primary endpoint of 24-hour AUC_{NH3}.
2) Sponsor proposed, for the primary efficacy analysis of ratio of AUC_{NH3} of Ravicti/sodium phenylbutyrate, that the upper bound for the confidence interval to define success would be (b) (4), instead of 1.25.
3) The FDA disagreed with the proposed upper bound, stating it should be 1.25.

SPA Agreement Letter issued on June 30, 2009:

1) The trial would only enroll adults.
2) The primary endpoint was 24-hour AUC for venous NH3 at the end of treatment with each drug (Days 14 and 28). The primary efficacy analysis was the ratio of the AUC_{NH3} geometric means of Ravicti/sodium phenylbutyrate, with an upper bound of the confidence interval not exceeding 1.25 (utilizing a 1-sided alpha of 0.025) constituting evidence of efficacy.

SPA Protocol Amendment submitted on March 19, 2010 (review filed on June 30, 2010):

1) The sponsor propose (b) (4)
2) The FDA did not agree with the amendment and said that it would result in nullification of the SPA. The pediatric data from Study 005 revealed substantive differences in PK profiles between pediatric patients and the adults in Study 003 (adult PK study). Of particular concern, from a safety standpoint, was the apparent higher PAA exposure in children relative to adults. In addition, Study 005 showed differences in the PK profile between Ravicti and sodium phenylbutyrate. The table below summarizes the data that were bases for these concerns (reproduced from the clinical review in the regulatory file, dated June 30, 2010):

Table 1: PK Comparison of Adult (UP 1204-003) vs. Pediatrics (HPN-100-005) UCD Subjects

PK Parameter	NaPBA		HPN-100	
	Adults UP 1204-003 (N=10)	Peds HPN-100-005 (N=11)	Adults UP 1204-003 (N=10)	Peds HPN-100-005 (N=11)
PBA in Plasma				
AUC_{0-24} (µg·h/mL)	739 (49.2)	236 (105.2)	540 (60.1)	631 (44.9)
$Cmax_{ss}$ (µg/mL)	141 (44.3)	37.4 (101.6)	70.1 (64.7)	95.6 (42.0)
$Cmin_{ss}$ (µg/mL)	0.588 (255)	0.366 (171.3)	2.87 (265)	1.50 (99.8)
PAA in Plasma				
AUC_{0-24} (µg·h/mL)	595.6 (123.9)	773 (73.3)	574.6 (168.9)	964 (63.6)
$Cmax_{ss}$ (µg/mL)	53.0 (94.7)	75.1 (64.4)	40.5 (147.6)	90.5 (69.1)
$Cmin_{ss}$ (µg/mL)	3.56 (194.4)	0.674 (130.5)	7.06 (310.7)	2.99 (122.1)
PAGN in Plasma				
AUC_{0-24} (µg·h/mL)	1133 (31.1)	1015 (44.7)	1098 (44.2)	1378 (40.2)
$Cmax_{ss}$ (µg/mL)	83.3 (25.8)	74.8 (37.3)	71.9 (56.0)	105 (33.5)
$Cmin_{ss}$ (µg/mL)	16.8 (86.1)	4.63 (66.4)	12.1 (134.4)	13.1 (64.9)

Pre-NDA Meeting December 7, 2010:

1) FDA expressed concern that the sponsor's NDA package, as outlined in the meeting backgrounder, would not provide adequate pediatric information, specifically information to support dosing in children under the age of 6 years and limited characterization of PAA levels in patients 6 years to 17 years of age.
2) The sponsor proposed (b) (4) The FDA could not agree with this proposal in light of the EOP2 recommendation of a safety data base that included 35-40 patients with 12 months of safety data at the time of NDA submission.
3) (b) (4) identification of an appropriate pediatric dose and evaluation of safety is necessary in light of the number of pediatric UCD patients who would be administered the drug once it is approved.

Written answers issued to questions (submitted by sponsor in a February 2011 meeting request) on August 3, 2011:

1) FDA provided comments on the pharmacokinetic model.
2) Sponsor proposed to include a (b) (4)

(b) (4)

3) FDA reiterated its recommendation that the sponsor provide data to support dosing in children under the age of 6 years of age in the NDA submission, stating, "Submission of a Risk Evaluation and Mitigation Strategy (REMS) would not satisfy nor replace the need for information in this patient population. Again, as stated in the meeting, this population constitutes a significant portion of the UCD population and would likely use your product, if approved. Therefore, we again strongly recommend that you provide this information at the time of your NDA submission. It may be acceptable for you to submit the PK results from Study HPN-100-012 for review at the time of the NDA submission to provide information on dosing in patients younger than 6 years of age. However, if these data suggest substantially different exposures compared to adults, additional safety data from the 12-month open label extension study may also be required."

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer this NDA provided "sufficient information to assure identity, strength, purity, and quality of the drug product, Ravicti liquid for oral administration." The manufacturing site inspections were acceptable. I concur with the CMC reviewers that the product should be described as an "oral liquid" in the product label, instead of an "oral solution". The product is not a substance that has been dissolved into a solution. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

I concur that the nonclinical studies support labeling consistent with the requirements for Pregnancy Category C.

Carcinogenicity. The results of a 2-year carcinogenicity study in rats (administered glycerol phenylbutyrate) were presented to the CAC on July 17, 2012, and the Committee concluded that tumors observed in the study were drug related. Multiple tumor types were observed, arising in the pancreas (acinar cell adenoma, carcinoma and combined adenoma/carcinoma) in males and females, Zymbal's gland (carcinoma) in males and females, adrenal cortex (combined adenoma/carcinoma) in females, uterus (endometrial stromal polyp and combined polyp/sarcoma), and thyroid (follicular cell adenoma, carcinoma and combined adenoma/carcinoma) in females. As noted in the Nonclinical Pharmacology review and the CDTL review, the doses administered in this carcinogenicity study ranged 3-8 times the exposure expected in human patients being treated for underlying UCD [range depends on sex and age (adult/pediatric)].

The Pharmacology reviewers concluded that even with the positive carcinogenicity study, the risk/benefit of Ravicti favored its approval. The CDTL concurred after considering: 1) an OSE consult review, 2) whether carcinogenicity would only be expected with the glycerol phenylbutyrate product (and not the currently marketed sodium phenylbutyrate product), and 3) the benefit associated with phenylbutyrate in managing ammonia levels in patients with UCD.

OSE's Division of Pharmacovigilance was consulted to evaluate whether there have been spontaneous reports of malignancy associated with Buphenyl (sodium phenylbutyrate). No reports were identified in the AERS database and in an NIH PubMed search; however, a signal of malignancy would be difficult to detect from these sources. My PubMed search for published evidence of increased risk of tumors in patients with UCDs, which had not necessarily been linked to their medications, found only limited information. A Japanese publication pointed to a case series of 8 cases of hepatocellular carcinoma in 56 adult patients with citrullenemia due to argininosuccinate synthetase deficiency (Nakayama M, et al. Hepatology, 1990; 11(5):819-23). In addition, Wilson, et al. (Molecular Genetics and Metabolism 105, 2012: 263-265) reported a possible association of UCDs with liver dysfunction, which they linked to an increased risk of developing hepatocellular carcinoma. The authors examined charts from the Children's Hospital Colorado longitudinal study site for the NIH-funded Rare Diseases Clinical Research Center longitudinal study of UCDs and found that more than 50% of patients at that site with symptomatic OTCD had liver dysfunction or failure. The authors cited prior publications that had documented acute liver dysfunction as a clinical presentation of ornithine transcarbamylase deficiency (OTCD). The authors linked these liver dysfunction signals and hepatocellular carcinoma to the underlying disease, and not the patients' medications. In addition, the medical history was reported in detail in some of the patients, which indicated they had not been exposed to phenylbutyrate.

The Buphenyl label does not contain carcinogenicity study information, and it appears it was approved in the absence of the existence of such information. Buphenyl is sodium phenylbutyrate, and while it is unlikely that the carcinogenicity study of sodium phenylbutyrate would differ from Ravicti, based on the presence of the glycerol component in Ravicti, that possibility cannot be completely excluded without actual data from a sodium phenylbutyrate carcinogenicity study. However, the phenylbutyrate is released from the glycerol backbone primarily within the gut lumen, so the drug to which both patients and rats are primarily systemically exposed is the same between Buphenyl and Ravicti (like UCD patients, intact glycerol phenylbutyrate was not detected in blood in rat PK studies). In addition, the Clinical Pharmacology review found that intact Ravicti was not detected in pharmacokinetic analyses of samples taken from UCD patients. (Although it was detected in normal volunteers, the applicant attributed the difference in presence of intact drug between populations to contamination during processing of the samples in the healthy volunteer study. Refer to the Clinical Pharmacology review for more detailed information.)

I concur with the reviewers that the risk/benefit of Ravicti for this issue still favors its approval. However, the same risk/benefit assessment does not apply to a breastfeeding infant who doesn't have UCD (if the infant's mother is taking Ravicti for her own UCD). The Maternal Health team was consulted regarding this issue and they contributed to evaluating the

label to assure that appropriate language was included in the Nursing Mother section. In addition, the Maternal Health team and Pediatric Ethics consultants worked with the Division to develop a PMR to evaluate breast milk for levels of exposure to phenylbutyrate and its metabolites.

Nonclinical hepatic histopathology review. In light of the literature search results regarding liver dysfunction, cited above, I examined the Pharmacology/Toxicology review for evidence of hepatotoxicity associated with glycerol phenylbutyrate in the submitted nonclinical studies. The Pharmacology/Toxicology review states histopathology examinations in nonclinical studies "revealed hepatocellular hypertrophy in 13-week oral toxicity studies in mice and monkeys and in a 52-week oral toxicity study in monkeys" (in which the hypertrophy increased with increasing doses). Mild mixed cellular infiltrates in liver were observed in a neonatal rat toxicity study. The histological description in the 12 month monkey study was "hypertrophy was characterized by enlarged hepatocytes with stippled to granular eosinophilic cytoplasm that compressed and constricted sinusoidal spaces without evidence of passive congestion or ischemia." I discussed those findings with the reviewers, and the Nonclinical Pharmacology team leader advised me that hepatocellular hypertrophy is assumed to be indicative of enzyme induction, and not classic evidence of a strong potential that the drug is a hepatotoxin in humans

Buphenly label subcutaneous PAA study. Another issue raised in the Pharmacology/Toxicology and CDTL reviews, and addressed in labeling discussions, is the presence of a description of neurotoxicity observed in a nonclinical study in the Buphenyl label. In that study, rat pups were administered phenylacetate (PAA) subcutaneously. Decreased proliferation and increased loss of neurons, reduced myelin, retardation of cerebral synapse maturation, reduction of number of functioning nerve terminal in the cerebrum and impaired brain growth were observed. The reviewers initially favored inclusion of this information in the Ravicti product label. However, in discussions with the Maternal Health team reviewers, significant questions regarding the reliability of this information were raised, based on the following: 1) the study and its data were not available for review, 2) the methodology was not clear, 3) similar changes were not observed in the histopathology evaluation of the nervous system tissue in the nonclinical studies submitted for review in the current NDA, including studies in which neonatal rats were exposed to glycerol phenylbutyrate.

The relevance of the findings from the nonclinical PAA study referenced in the Buphenyl label was further examined by me, in the context of the neurotoxicity data from the nonclinical studies submitted in the Ravicti NDA. I considered:

1) In adult animal studies conducted with glycerol phenylbutyrate, central nervous system histopathology findings were unremarkable.
2) The Ravicti NDA included neonatal/juvenile rat studies [glycerol phenylbutyrate administered orally postnatal days 2-15, 2-34, 2-50, 2-12/7/129, and 2-gestation day 20 (females)]. Doses in these studies ranged 0.65 g/kg/day to 6 g/kg/day. In addition there was a peri-/postnatal rat study in which animals were administered oral drug at doses 0.3-0.9 g/kg/day from gestational day 7 to lactation day 20. Decreased brain weight was noted in an oral repeated dose toxicity study in

neonatal rats, but the other organ weights were also decreased. Beyond the histopathology examination of brain tissues in these studies, learning and memory tests were assessed with passive avoidance and water-filled M-Maze tests. The reviewer concluded that there were no clear treatment-related changes in learning ability in animals exposed to glycerol phenylbutyrate.

3) In a rat oral peri- and post-natal reproduction toxicity study, the F1 generation assessments included passive avoidance and water-filled M-maze tests and the reviewer concluded that there were no clear treatment-related changes in learning ability in these animals, based on data from these tests. (F1 generation exposure to drug did not continue after birth.)
4) In the oral repeated dose toxicity study in neonatal rats (QBU00007), 2-day old rats were treated with doses of 0.65 to 1.2 g/kg/day. CNS histopathological evaluation was performed. No unusual findings were reported. There was no evidence of treatment-related changes in learning and memory tests (passive avoidance and water maze tests). Decreased brain weight was noted, but the weights of other organs were also decreased.

The Pharmacology/Toxicology reviewer stated that he believed it was appropriate to keep the PAA study from the Buphenyl label in the label. The Pharmacology/Toxicology Team Leader has entered an addendum review to document his own position that it is appropriate to not include this information in the Ravicti label. Based on the findings of the review of the nonclinical studies submitted in this NDA and discussions regarding the limitations of our ability to critically evaluate the study presented in the Buphenyl label, I concurred with the Maternal Health Team's Toxicology reviewer and the Pharmacology/Toxicology Team leader's conclusion that the Buphenyl label study should not be included in the Ravicti label. The substantial nonclinical data reviewed in this NDA did not observe the same toxicity detected in animals administered PAA by subcutaneous route. The product label will state that there are clinical data that document the neurotoxicity of PAA and that monitoring of PAA levels should be considered for guiding dose adjustment.

5. Clinical Pharmacology

I concur with the Clinical Pharmacology reviewers' conclusions that there are no outstanding clinical pharmacology issues that preclude approval. The efficacy trial that provides the key evidence supporting approval, Study 006, is essentially a bioequivalence trial between Ravicti and the currently marketed sodium phenylbutyrate product, with the focus of the analysis being a PD marker of efficacy, venous ammonia 24 hour AUC. The clinical review team sought guidance from the Clinical Pharmacology reviewers regarding the endpoint and analysis plan for this key trial during the protocol development phase. The Clinical Pharmacology reviewers also carefully examined the data from this trial during the NDA review to assess efficacy and to evaluate dose recommendations. The efficacy data from Study 006 will be discussed in Section 7 Efficacy of this review. Please refer to the thorough Clinical Pharmacology reviews, the Statistical review and the CDTL summary review for details. In this section of my review I will focus on the major dosing issues identified during the review and how these were addressed in product labeling. These included: 1) establishing

a dose for the pediatric population, 2) establishing a starting dose for patients who are treatment naïve to phenylbutyrate, and 3) instructions for adjusting dose.

Pediatric dosing. As mentioned above, a major review issue identified even prior to NDA submission was whether there would be adequate data available in children to support defining doses for children across the full pediatric age range. The reviewers had noted that in children over the age of 2 years, there was higher variability and higher concentrations of PAA than in adults. The initial NDA submission included clinical trials in children over the age of 6 years, and the applicant submitted the results of a PK study in children under 6 years of age (in April 2012) after the NDA was filed. Review of the data from this younger pediatric group revealed that the available data points from sparse sampling in the 4 patients in the clinical data set who were less than 2 years of age were inadequate for establishing a safe dose. Modeling and simulation was considered unreliable, and two of the patients had PAA concentrations that exceeded 400 micrograms/ml (after both Ravicti and Buphenyl). In light of neurologic safety issues that are connected to both inadequate doses of Ravicti to manage serum ammonia, and excessive exposure to PAA active metabolite, which has been associated with neurotoxicity, the review team ultimately concluded that a safe dose could not be determined in children below the age of 2 years. For this reason, the label will state safety and effectiveness has not been established in children less than 2 years.

Refer to Section 8 Pediatrics of this review for a discussion of the pediatric population <2 months of age, for whom the product will be contraindicated due to the known immaturity of pancreatic function in this age group. It is not known whether there is adequate lipase activity in this age group to hydrolyze the phenylbutyrate from the glycerol backbone of Ravicti. Lack of efficacy to manage blood ammonia levels in this age group could be devastating.

Dosing recommendations for treatment naïve patients. As stated in the Clinical Pharmacology review, even for the adult population, "this development program was not designed to address the starting dose for Ravicti nor the dose titration strategy." Nearly all patients in this program were converted to a Ravicti (glycerol phenylbutyrate) dose based on the dose of Buphenyl (sodium phenylbutyrate) upon which they were already stable, using a mathematical formula. The product, once marketed, will be used in treatment naïve patients, and there were only six patients in the clinical development program who had Ravicti initiated without prior exposure to Buphenyl, all treated in an open label, single arm, long term safety trial. Two of those six patients had dose modifications prompted by treatment emergent adverse events and were removed from study prior to completion.

The reviewers considered not labeling the product with dose recommendations for treatment naïve patients, requiring that the patient first be treated with Buphenyl to establish the appropriate dose, and then convert that dose to the comparable Ravicti dose. However, the Buphenyl label is not precise in recommending an initial dose, and merely provides a dose range:

> "The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450 – 600 mg/kg/day in patients weighing less than 20 kg, or 9.9 – 13.0 g/m2/day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day)."

The reviewers ultimately determined that the Dosage and Administration section of the label should be divided into a dose section for patients who are being converted from a stable Buphenyl dose to Ravicti, and a separate section for treatment naïve patients. In all patients, the label will state that the maximum total daily dosage is 17.5 ml (no matter what the BSA calculation indicates). The Clinical Pharmacology reviewers recommended a dose range (4.5 to 11.2 mL/m^2/day) for the treatment naive population, based on the data from the patients in the NDA (who were converted from their stable dose of Buphenyl), within which the ultimate stable dose should lie. The product label will direct providers to start dosing at the low end of the range for certain populations, i.e., 4.5 mL/m^2/day) in patients with residual enzyme activity who are not adequately controlled with protein restriction. In addition, the reviewers worked with the Applicant to develop a general framework to consider when determining the starting dose, including the amount of dietary protein, the estimated amount of daily nitrogen from daily protein that is normally excreted, the amount of urinary PAGN that this amount correlates with, and the estimated dose that matches that targeted PAGN excretion. The label will merely provide this as a foundation from which to build an approach to identify a starting dose. The label will state that the individual's amount of residual enzyme activity must also be considered when estimating the starting dose.

Guidelines for dose modification. Finally, with regard to dose modification recommendations in product labeling, the applicant had proposed specific recommendations regarding utilization of PAA levels, U-PAGN levels and a specific PAA/PAGN ratio (b) (4) to guide dose modification decisions. (PAGN in the ratio is plasma PAGN.) Although the assays for PAA, PAGN and U-PAGN used in the clinical development program were considered adequately validated by the Clinical Pharmacology reviewers for use in the clinical trials, these assays have not been reviewed by CDRH for marketing purposes. The applicant has worked with a CLIA approved laboratory to assure availability of these assays upon request by clinicians. They plan to make Ravicti available through specialty pharmacies, which will in turn be a resource to prescribers to inform them where they can send samples for assay results. (b) (4)

.

The reviewers discussed this approach with staff from OMPT/CDRH/OIVD. The CDRH staff asked first for verification from the clinical reviewers that these assays are not required for the safe and effective use of the drug. The reviewers provided clarity that phenylbutyrate has been available for decades and that the key laboratory value needed for management is ammonia level. While these assays may have been available in local institutions to further assist dose decisions of clinicians caring for patients with UCD, they have not been generally available and the cornerstone to management of treatment with a nitrogen scavenger is the ammonia level. Based on this, the CDRH staff acknowledged that the applicant's approach to make these assays available via a CLIA approved laboratory was acceptable; however, they advised the reviewers that for the purposes of product labeling, specific target laboratory values should be avoided if they can't be definitively established based on the clinical trial data. In addition,

they recommended that labeling refer to these tests as tests that are available and may be helpful in the management of patients with UCDs being treated with this drug.

In light of the interaction with CDRH scientists, the reviewers determined that references to PAA and PAGN levels could be included in the label, with the following constraints: 1) When these assays are mentioned, the label should include language such as "if available" and 2) The language should be modified to assure that a definitive target level should not be included. If a target range is mentioned, the language should communicate some uncertainty about the range.

With these guiding principles, the reviewers recommended against specifically defining a PAA level to be avoided, since neurotoxicity symptoms occurred across a broad range, depending upon the population studied. Neurotoxicity symptoms occurred at a much lower PAA range in normal volunteers (with probability increasing when PAA levels exceed 80 micrograms/ml) than in a oncology study publication referenced by the applicant (source of the applicant's proposed target level to avoid of 500 microgram/ml). In fact, there was little correlation between PAA C_{max} levels and symptoms of neurotoxicity in the UCD patients studied in this NDA. The reviewers attributed this to the fact that nearly all patients were already on a stable dose of sodium phenylbutyrate when they entered the trial. They noted that UCD patients could have become tolerant to neurological toxicity symptoms. The reviewers recommended providing the scope of the clinical data across populations on the relationship of PAA levels to neurological adverse events in the product label. A prescriber should not dismiss the possibility that Ravicti is the source of neurological symptoms in a patient with serum ammonia level within normal range and a PAA level that is below 500 micrograms/ml.

The applicant strongly advocated for inclusion of a specific PAA/PAGN ratio (exceeds (b) (4) in the product label, for use as a dose modification guideline. Their position was that high PAA variability over a 24 hour period, makes it likely that a single PAA level assessment in a 24 hour period will under-represent the individual patient's actual maximum exposure to this metabolite. They proposed that their data analyses indicate that if the ratio is utilized (adjusting for PAGN level), even a "low" PAA level could predict excursion into the higher range that is more likely to be associated with neurological toxicity symptoms during 24 hours. This ratio would reflect lower relative conjugation of the PAA to glutamine for excretion, which means that during the course of a 24 hour period a patient would have higher than necessary PAA exposures.

The Clinical Pharmacology and Clinical reviewers concurred that PAA and U-PAGN levels could be important in optimally managing an individual patient. The Clinical Pharmacology reviewer could not agree that a specific PAA/PAGN(plasma) ratio had been appropriately established that could serve as the "cut point" that should be applied to all patients to definitively guide dose adjustments. They noted that the analyses submitted to support a (b) (4) "cut point" for the ratio were based on selection of a specific PAA level of 500 micrograms/ml as the absolute level to be avoided for associated neurotoxicity. The Clinical Pharmacology reviewers reiterated that the absolute PAA level that is associated with neurotoxicity has not yet been adequately established for the purposes of labeling. The applicant utilized 500 micrograms/ml in a model to establish an absolute ratio value to guide dose modifications for labeling purposes. The positive predictive value for 500 micrograms/ml was relatively low.

Ultimately, the Clinical Pharmacology reviewer recommended the language in the Dose Adjustment and Monitoring section of the product label should be general, as follows:

> **Adjustment based on Plasma Ammonia**: Adjust the RAVICTI dosage to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) according to age.
>
> **Adjustment Based on Urinary Phenylacetylglutamine**: If available, U-PAGN measurements may be used to help guide RAVICTI dose adjustment. Each gram of U-PAGN excreted over 24 hours covers waste nitrogen generated from 1.4 grams of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the ULN, the RAVICTI dose should be adjusted upward. The amount of dose adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-h U-PAGN level and the estimated RAVICTI dose needed per gram of dietary protein ingested and the maximum total daily dosage i.e. 17.5 mL.
>
> Consider a patient's use of concomitant medications, such as probenecid, when making dosage adjustment decisions based on U-PAGN. Probenecid may result in a decrease of the urinary excretion of PAGN [see *Drug Interactions (7.2)*].
>
> **Adjustment Based on Plasma Phenylacetate:** If available, measurements of the plasma PAA levels may be useful to guide dosing if symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or intercurrent illness. Ammonia levels must be monitored closely when changing the dose of RAVICTI. The ratio of PAA to PAGN in plasma may provide additional information to assist in dose adjustment decisions. In patients with a high PAA to PAGN ratio, a further increase in RAVICTI dose may not increase PAGN formation, even if plasma PAA concentrations are increased, due to saturation of the conjugation reaction. The PAA to PAGN ratio has been observed to be generally less than 1 in patients without significant PAA accumulation. [*see Warnings and Precautions (5.1)*].

Note: The Clinical Pharmacology verified the conversions specified in the label, and provided the following background details for the conversions found in the product label's Dosage and Administration section:

RAVICTI dose / g protein calculation

Assumptions: 1) Nitrogen content in protein : 16%
2) Waste nitrogen: 47%
3) PBA conversion to PAGN: 70%

Based on these assumptions, the following calculations were performed based on 100 g protein consumption:

100 g protein ==> 16 g nitrogen

7.5 g waste nitrogen arises 16 g nitrogen

7.5 g nitrogen ==> 0.53 M

2 mole nitrogen per one mole PAGN ==> 0.27 M PAGN

0.27 M PAGN = 0.27 M PBA=0.09M glycerol PBA g
0.09M glycerol PBA=48.24 g glycerol PBA=44 ml RAVICTI

If 100% PBA converts to PAGN, 0.44 ml RAVICTI is needed to cover nitrogen waste from 1 g protein

> With approximately 70% conversion, 0.63 ml RAVICTI is needed for 1 g protein. Therefore, it is estimated that a 0.6 ml RAVICTI dose is needed per 1 g protein. (This does not take into account the patient's residual enzyme activity.)

Cardiac electrophysiology evaluation. A final review issue was the thorough QT study submitted in this application. The applicant strongly advocated for inclusion of detailed data from this study in the product label. The tQT reviewer agreed that the largest upper bounds of the 2-sided 90% CI for the mean difference between Ravicti 13.2 g/day and placebo and between Ravicti 19.8g/day and placebo were -0.7 ms and -1.3 ms, respectively. However, the tQT team took a firm position that the study was inadequate because the moxifloxacin time profile was not consistent with the time course expected for moxifloxacin. They further commented that the supratherapeutic exposure achieved in the study did not cover the level of exposure that might be reached in patients with hepatic impairment, and they noted that the ECG measurements were only sparse (8, 12, 16 hours) around the day's peak concentration time for metabolites (12 hours from the time of first does on day 3). The latter was considered a suboptimal sampling scheme. The tQT review team recommended that the applicant repeat the thorough QT study.

The Clinical reviewers questioned the necessity of repeating the study and asked if the QT study data could provide assurance that a certain degree of QT prolongation associated with Ravicti could be excluded. The tQT reviewers acknowledged that this study provides assurance that the drug is unlikely to cause large QT prolongation effects (in range of 10-20 ms). In light of this, the Clinical team has recommended that the applicant should not be required to repeat the study. I concur. The tQT team recommended language for the product label as follows:

> "The upper bound of the one-sided 95% confidence interval (CI) for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) for RAVICTI was below 10 ms. However, assay sensitivity was not established in this study because the moxifloxacin time-profile was not consistent with expectation. Therefore, an increase in mean QTc interval of 10 ms cannot be ruled out."

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The Clinical, Statistical and Clinical Pharmacology reviewers all concurred that Study 006, the major efficacy trial submitted to support this NDA, established that Ravicti (glycerol phenylbutyrate) is noninferior to the approved sodium phenylbutyrate product in control of serum ammonia, as measured by AUC_{NH3} over 24 hours. The details of the study design can be found in their reviews. Although both Ravicti and the comparator are phenylbutyrate products, an approval path based on bioequivalence of phenylbutyrate was not possible

because the pharmacokinetics of the two drugs differed. The ratio of geometric means for 24 hour AUC_{NH3} fell well below the prespecified upper bound of the confidence interval of 1.25. This is summarized in the table below, reproduced from the Clinical Pharmacology review.

Table 2. Non-Inferiority Analysis of Venous Ammonia AUC0-24 (ITT Population)

Blood Ammonia$_{0\text{-}24}$ 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)

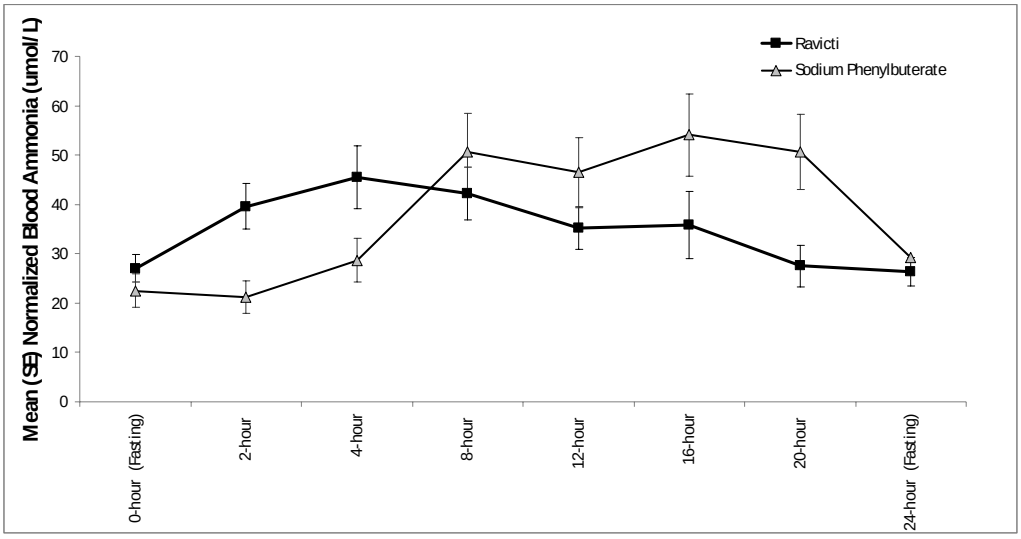
Source: modified from Table 15 in CSR HPN-100-006

[a] Individual missing NH3 AUC data were imputed if values were missing at 0 or 24 h or the patient had < 12 h of venous ammonia data.

[b] Results on original scale were obtained by exponentiating the corresponding log-transformed results.

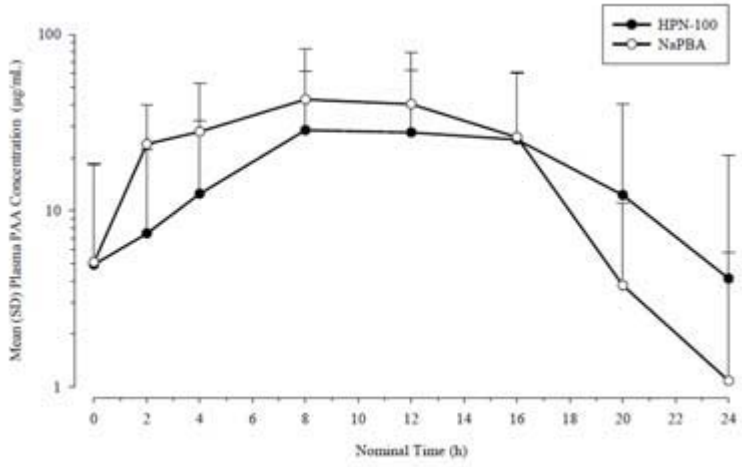
Although the geometric means of the AUC_{NH3} fell below the prespecified upper bound of 1.25, the differences in the PK of the drugs do impact the pharmacodynamic effects by time over a 24 hour period, which is clearly demonstrated with the figure below. This figure will be included in product labeling to communicate the relative patterns of NH_3 control.

Figure 2: Short-Term Venous Ammonia Response in Adult UCD Patients (Study 006)



The following figure, taken from the Clinical Pharmacology review summarizes the PAA concentrations associated with the two drugs over the 24 hour period that resulted in the NH3 levels summarized above.

Figure 3. Mean (+SD) PAA Plasma Concentration-Time Profiles of HPN-100 (Ravicti) and NaPBA in Study 006



The pharmacokinetic data for Ravicti and Buphenyl indicate that phenylbutyrate is more slowly absorbed after Ravicti administration than Buphenyl, presumably due to time needed to release phenylbutyrate from the glycerol backbone.

Section 14 Clinical Studies of the product label will include a subsection that describes the efficacy observed in Study 006 (the major efficacy trial). The adult data from the uncontrolled open label 12 month study will also be presented (51 adults) and will include a statement that the mean venous ammonia levels were within normal limits during the 12 month study. In addition the label will state that 7/51 of the adults reported a total of 10 hyperammonemic crises during the 12 month period.

As mentioned earlier, the adequacy of the dataset to establish an indication for each of the various UCDs and to establish a safe and effective dose for children at ages across the entire pediatric age range were major review issues. The following table summarizes the trials submitted to support the NDA, and includes the number of patients by age group and UCD subtype.

Study Number	Phase	Design	Objective	Population (Age/UCD subtype)	Gender
UP 1204-003	2	Non-R, OL, fixed-sequence, switch-over	Safety and efficacy	**Adult** UCD OTC=8 ASS=1 HHH=1	Male=4 Female =6
HPN-100-005	2	Non-R, OL, fixed-sequence, switch-over followed by a 12 month OL phase	Safety and efficacy	**Pediatric** UCD Ages 6 years-17 years OTC=9 ASL=1	Male=1 Female =11

				ASS=1 Switch over: 6y-11 years = 7 12-17 years = 4 Extension: 6y-11 years = 11 12-17 years = 4	
HPN-100-006	3	R, DB, X	Safety and efficacy	**Adult** UCD OTC=40 ASS=2 CPSI=2	Male=13 Female=31
HPN-100-007	3	Uncontrolled [Extension **to 006** + enrolled additional patients]	Safety	**Adult and Pediatric UCD** ≥ 6 years <18 years = 9 Adults = 51 (40 adults had been treated in Study 006) OTC=82%	Male=19 Female =41
HPN-100-011	2	Uncontrolled Patients completing HPN-100-**007** + HPN-100-**005** enrolled for continued access to drug Safety extension	Safety	Adult and Pediatric 6-11 years= 17 12-17 years = 7 Age 18+ years = 43	Male=20 Female=47
HPN-100-012 switch-over	2	Non-R, OL, switch-over	PK Safety	**Pediatric** UCD <6 years of age OTC=3 ASL=8 ASS=3 ARG=1 29 days to <2 years =4 2y to 6y = 11	Male=8 Female=7
HPN-100-012 Safety extension	2	OL, safety extension of 012	Safety and efficacy	Pediatric UCD <6 years of age OTC = 5 ASL = 10 ASS = 6 ARG = 1 2 mo ->2 years = 4 2 y - <6 years = 19	Male=11 Female =11

The trial data from cross over and long term open label Ravicti administration in pediatric patients 2 years of age and older were considered adequate by the Clinical Pharmacology reviewers to define a safe and effective dose in this subpopulation. The data from patients ages 2 years to 17 years enrolled in the clinical trials will be presented in a separate subsection of the product label's Section 14 Clinical Studies, The AUC_{NH3} data for Ravicti and sodium

phenylbutyrate from the two short term switch over pediatric trials (Studies 005 and 012, with latter data limited to those from children 2 years to 6 years of age) will be presented, along with a figure describing the mean venous ammonia levels over a 24 hour period on each of the drugs (pooled data).

The long term uncontrolled pediatric extension study data will also be described. It is important to note that 12 month serum ammonia data were only available to review from children ages 6 years and older. Interim data from the long term study in younger children were submitted in the 120 day safety report. While the reviewers had adequate short term data to define a safe dose for children between the ages of 2 years and 6 years, the median follow up of the long term trial enrolling children less than 6 years was 4.5 months at the time of the interim look. Similar to the adult subsection, the pediatric subsection 14.2 of the label will state that the mean fasting venous ammonia values were within normal limits during long-term treatment with Ravicti, and will state that 5/26 pediatric patients ages 6 years to 17 years had a total of 5 hyperammonemic crises. The data presented in the label from the long term study in children 2 years through 5 years of age will be limited to the number of hyperammonemic crises that had been observed in the study at a median time on study of 4.5 months (3 crises in 2/16 patients).

I concur with the CDTL that the neurocognitive assessment data obtained in the clinical trials should not be included in product labeling. There was no control arm and no formal hypothesis testing prespecified. These data are exploratory and can only be viewed as hypothesis generating.

No clear impact of UCD subtype on Ravicti efficacy was detected in the clinical trial data. As described earlier in this review, the review team recommended against labeling for specific subtypes of UCDs; however, because the risks of neurotoxicity and carcinogenicity can't be justified if a patient can be adequately managed on dietary and other standard measures appropriate to their UCD subtype and individual phenotype, the indication will state:

> RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).
> Limitations of Use:
> RAVICTI is not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly acting interventions are essential to reduce plasma ammonia levels.
> The safety and efficacy of RAVICTI for the treatment of *N*-acetylglutamate synthase (NAGS) deficiency has not been established.
> The use of RAVICTI in patients <2 months of age is contraindicated [see *Contraindications (4)*].

6. Safety

The size of the safety database is described by the CDTL in her review. The number of patients exposed to drug for at least 12 months meets the number recommended by the FDA during pre-NDA discussions. The following is a quote from the CDTL review:

> "The safety database for Ravicti includes data from 9 controlled and 3 uncontrolled clinical studies in 268 subjects who received at least one dose of HPN-100. These subjects included 112 UCD patients (65 adults, 26 children between the ages of 6 and 17 years and 22 patients < 6 years old) with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH across five studies (UP 1204-003, HPN-100-005, HPN-100-006, HPN-100-007, and HPN-100-012SE)…. Safety data is also available for 39 patients without UCDs who had hepatic impairment from two studies (UP 1204-002, HPN-100-008 Part A) and 130 healthy adults, including 32 enrolled in two Phase 1 single- and multiple-dose pharmacokinetic(PK) / pharmacodynamic(PD) studies (UP 1204-001, UP 1204-002) and 98 enrolled in a thorough QT/QTc study (HPN-100-010).
>
> 77 patients with UCDs have completed 12 months of HPN-100 as of the time of original submission of the NDA (51 adults from HPN-100-006, 26 pediatric patients age 6-17 years). Most of these patients (43 adults and 24 pediatrics age 6-17 years) are now enrolled in the continuing access protocol, HPN-100-011."

There were no deaths in the UCD trials. Deaths (n=5) in the hepatic impairment study (patients without a diagnosis of UCD) were described as death from hepatic failure, gastrointestinal hemorrhage and acute renal failure. The investigators considered all but one to be unrelated to study drug. One investigator considered the liver failure that led to death in one of the patients as possibly related to study drug. The reviewers could not exclude that Ravicti had worsened the complications of hepatic disease in all of these patients.

The most common adverse reactions in the safety data base for the short term adult efficacy trial (Study 006) were diarrhea, flatulence and headache. The following table will be included in the product label summarizing the short term safety findings from the adult controlled trial.

Table 3: Adverse Reactions Reported in ≥ 2 Adult UCD Patients in Study 006

	Number (%) of Patients in Study 1	
	Sodium Phenylbutyrate (N = 45)	**RAVICTI (N = 44)**
Gastrointestinal disorders		
Abdominal discomfort	3 (7)	0
Abdominal pain	2 (4)	3 (7)
Diarrhea	3 (7)	7 (16)
Dyspepsia	3 (7)	2 (5)
Flatulence	1 (2)	6 (14)
Nausea	3 (7)	1 (2)
Vomiting	2 (4)	3 (7)
General disorders and administration site conditions		
Fatigue	1 (2)	3 (7)
Investigations		
Ammonia increased	1 (2)	2 (5)
Metabolism and nutrition disorders		
Decreased appetite	2 (4)	3 (7)

	Number (%) of Patients in Study 1	
	Sodium Phenylbutyrate (N = 45)	**RAVICTI (N = 44)**
Nervous system disorders		
Dizziness	4 (9)	0
Headache	4 (9)	6 (14)

In the long term, uncontrolled safety extensions, adverse events reported in >10% of adult patients included diarrhea, nausea, vomiting, decreased appetite, fatigue, hyperammonemia, dizziness, headache, and symptoms of respiratory infections. In pediatric patients, adverse events that occurred in >10% included diarrhea, nausea, vomiting, decreased appetite, headache, hyperammonemia, and respiratory tract infection. In both adult and pediatric patients, the Clinical reviewers did not consider the respiratory infections and symptoms of respiratory infections treatment related. For this reason, these were not included in the final product labeling.

The reviewers did not identify changes in liver enzymes or bilirubin that they considered evidence of clinically meaningful hepatotoxicity in the short term trials. The Clinical reviewer noted in her review that in the long-term, uncontrolled open label studies, " 5% of laboratory AEs were for elevations of ALT, 6% elevations of AST and 1.3% elevations in bilirubin." The Clinical reviewer reported in email communication that she found no cases of Hy's Law. The following shift table is reproduced from the Clinical Review. There were numerically more patients who shifted from high baseline ALT and AST to normal than vice versa. However, nearly all patients were on phenylbutyrate when they entered these trials. The Clinical reviewer noted that one of the patients who shifted from normal baseline bilirubin to high had started a new (for the patient) concomitant antiepileptic medication Keppra (levetiracetam), which carries labeling regarding "abnormal liver function test, hepatic failure, hepatitis" in the section "Postmarketing Experience." In addition, in one of the patients, shifts to high AST and ALT were attributed to concomitant use of risperidone and methylphenidate.

Table 4: Change from Baseline and Shifts in Transaminases, Bilirubin, Alkaline phosphatase and Albumin in Long-Term Open-Label Studies HPN-100

	Change from Baseline		Shifts from Baseline		Reported as an AE
			High→Normal	Normal→High	
Parameter	n	Mean	n/N (%)	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	

One patient had ventricular fibrillation that occurred during a liver transplantation, a day after stopping Ravicti. This was an SAE; however, the reviewers did not consider the event clearly attributable to Ravicti in light of the concomitant circumstances, i.e., liver transplantation, which would have been associated with significant cardiophysiologic stress and medications that could have affected cardiac electrophysiology, including anesthetic drugs and opioids.

In summary, I concur with the reviewers that there are no safety issues that should preclude the approval of Ravicti. I concur that a REMS is not necessary, and that the labeling with a non-REMS Medication Guide is adequate to manage risks. (See further discussion regarding the REMS proposed by the applicant at the time of NDA submission in Section 8 Pediatrics of this review.) Discussion of PMRs that will be required as a condition of approval under FDAAA to address safety issues in the pediatric population can also be found in Section 8 Pediatrics, below. In addition to the trials listed there, the applicant will be required to conduct a trial to further characterize the safety and efficacy of initiating treatment in treatment naïve patients. As discussed in Section 5 Clinical Pharmacology, there were only 6 treatment naïve patients in the trials submitted for review, and 2 of the six experienced treatment emergent adverse events. While the review team ultimately concurred that the product approval should not be limited to patients who have been stabilized on sodium phenylbutyrate, questions remain about

whether initiating treatment in treatment naive patients as described in the product label could be further optimized to improve the safe and effective use of Ravict in these patients. The trial will be described as follows in the letter:

2013-4 A randomized, controlled clinical trial to assess the safety and efficacy of Ravicti (glycerol phenylbutyrate) in patients with Urea Cycle Disorders who are treatment naïve to phenylbutyrate.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	August 2013
Trial Completion:	June 2016
Final Report Submission:	March 2017

7. Advisory Committee Meeting

An advisory committee meeting was not held because Ravicti is not a new molecular entity, there were no safety concerns, and its primary efficacy endpoint was met.

8. Pediatrics

As stated earlier in this review, Ravicti received orphan designation for the condition urea cycle disorders. Therefore, PREA does not apply. However, since UCDs frequently present in infancy and early childhood, being able to provide pediatric labeling was of great importance to the review team, both during clinical development of Ravicti, and in reviewing the NDA. Key review issues discussed previously in this review were the limited information available to support a safe dose for infants < 2 months and for young children between 2 months and 2 years of age. In addition, there were safety concerns raised regarding potential exposure of infants without a diagnosis of UCD to Ravicti in breast milk (if the nursing mother is taking Ravicti). I will discuss those issues sequentially in this section.

Infants less than 2 months of age. The applicant was asked to submit information to address the review team's concerns that immature pancreatic function in infants less than 2 months of age could negatively impact the efficacy of Ravicti. The applicant stated, "Measurements of fat absorption in newborns confirms that digestion of fat during early neonatal life varies widely, ranging from nil to nearly normal adult levels, and that the newborn's ability to digest fats generally matures rapidly to normal adult levels during the first two months of life.[1]" The article by Manson et al used a C-labeled mixed triglyceride (MTG) to show that neonates have a limited capacity to digest dietary fat and that a rapid maturation in intraluminal fat digestion during the early months of life. The publication also described the use of a stable isotope

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

breath test (the MTG breath test) as a simple, reproducible, non-invasive way of measuring the development of fat digestion in early life.[2]"

The review team met with members of the Pediatric and Maternal Health Staff, in addition to Pediatric Ethicists from the Office of the Commissioner to discuss whether it is appropriate to contraindicate use of Ravicti in infants <2 months of age. While there was consensus that information in the literature on infant pancreatic function made these safety concerns more than just theoretical, the reviewers acknowledged that it was unknown whether infants might have sufficient lipase function from nonpancreatic sources to release phenylbutyrate from the glycerol backbone. In addition, it is unknown how much pancreatic lipase must to be present to achieve an effective release of phenylbutyrate. The Clinical pharmacology review presents the following *in vitro* data on hydrolysis of glycerol phenylbutyrate by various lipases:

> "In vitro, HPN-100 is hydrolyzed by lipases such as pancreatic triglyceride lipase (PTL), carboxyl ester lipase (CEL) and pancreatic lipase related protein 2 (PLRP2). The specific activity was determined by µmole fatty acid released/min/mg protein or Units/mg. The specific activity for HPN-100 was in order of PTL (~600 Units/mg), CEL (250 Units/mg) and PLRP2 (22 Units/mg) suggesting potentially predominant role of PTL and of CEL to a lesser degree, in hydrolysis of HPN-100 (Table 15).

Lipase	Bile Acid/Salt	Mean Units/mg Lipase	
		With Colipase	Without Colipase
PTL (3 µg)	NaTDC (0.5 mM)	618	342
PLRP2 (20 µg)		35	32.2
PTL (3 µg)	NaTDC (4 mM)	592	42
PLRP2 (20 µg)		22	10.8
CEL (10 µg)	NaCholate (10 mM)	249	

CEL = carboxyl ester lipase; GPB = glycerol phenylbutyrate; NaCholate = sodium cholate; NaTDC = sodium taurodeoxycholate; PLRP2 = pancreatic lipase related protein 2; PTL = pancreatic triglyceride lipase.
* µmol fatty acid released/min/mg protein or Units/mg

> ***Reviewer's comments:*** PTL likely makes a dominant contribution to the absorption of HPN-100 in adults, but is lacking during the early neonatal period. Since PLRP2 and perhaps CEL are both believed to play an important role in digestion of fats during the neonatal period and prior to developmental expression of PTL, the present findings suggest that the combined activities of PLRP2 and CEL might also digest HPN-100 in newborns. PTL converts triglyceride substrates found in ingested oils to monoglycerides and free fatty acids."

Ultimately, the reviewers concluded a Contraindication was appropriate, for reasons discussed above and in the Introduction to this review. There was significant concern that there would be inadvertent substitution of Ravicti for sodium phenylbutyrate in infants, a medication error that could be devastating if the infant does not have adequate lipase function to release the phenylbutyrate from the glycerol backbone. The reviewers concurred that a trial was needed to

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

answer the question regarding whether the available lipase activity in neonates is sufficient for Ravicti to be efficacious. The Pediatric Ethics consultants concurred that this question was an important question to answer and that based on the available information, it could be ethically conducted, as long as appropriate monitoring was incorporated in the trial design. A major concern addressed in these discussions was whether such a trial could receive IRB approval when the product was contraindicated in the population. The Pediatric Ethics consultants advised that IRB approval would be possible as long as the product label contained sufficient information to explain the reason for the contraindication. That information would provide support for conducting the trial in a controlled setting with appropriate monitoring. This information is provided in the Contraindication and Section 8.4 of the label.

Patients ages 2 months to < 2 years. During the clinical development of Ravicti, the FDA became concerned that the applicant would not submit pediatric data with the NDA that would support product labeling. This was of critical importance to the FDA because UCDs are diagnosed in very young children and the product was being developed as more palatable formulation of phenylbutyrate, which would make the prescriber want to use it in young children. Based on these concerns, during pre-NDA clinical development interactions with the sponsor, the Division asked that they plan to submit a REMS with the NDA if sufficient pediatric data were unavailable to support a safe and effective dose in children at the time of NDA submission. The Division was concerned that a REMS might be needed to assure that Ravicti would not be used in children if there were inadequate data to support dosing and if available data suggested a substantive risk of PAA toxicity in children. The Division had also informed Hyperion that if they submitted data for children between ages 29 days and 5 years, a REMS might not be needed. The applicant submitted a REMS that consisted of:

The reviewers determined that the additional pediatric data submitted during the course of the review was adequate to establish a safe and effective dose for pediatric patients ≥ 2 years of age. A decision was made by DRISK in conjunction with DGIEP and the REMS Oversight Committee (ROC) (email communication dated September 26, 2012) that a REMS for Ravicti is not necessary to ensure that benefits outweigh the risks of Ravicti treatment. After review of the complete submission, the reviewers concluded that risks can be managed through labeling, routine pharmacovigilance, and a non-REMS Medication Guide. Knowledge gaps in

infants <2 months will be managed with a Contraindication. The knowledge gap in children <2 years will be managed with standard pediatric language utilized when there are inadequate data to establish the safe and effective dose of the product. Although the data presented were inadequate to give definitive dose guidelines in this subgroup, there was insufficient cause for invoking a REMS to restrict treatment to use of sodium phenylbutyrate in this age group. These patients are currently managed with sodium phenylbutyrate, and it might be possible to safely convert them from their sodium phenylbutyrate dose to Ravicti. However, we don't currently have adequate data to definitively state this in the product label.

Nursing mothers. Consultants from the Maternal Health Staff were asked to review the Pregnancy labeling section of the proposed product label and the Nursing mother's section. Their recommendations for revisions were incorporated in the final product label and Medication Guide. The consultants met with the review team to discuss the proposed PMR study to study drug levels in human breast milk. The Pediatrics Ethics consultants were also invited to this meeting. There was consensus that knowing whether the drug enters breast milk is important information for mothers with UCD who are nursing an infant. Ravicti is carcinogenic and the active metabolite PAA is neurotoxic. The consultants agreed that the proposed PMR trial could be ethically performed, as long as appropriate measures were built into the protocol to assure that healthy infants are not exposed to the breast milk from women participating in the study, and if mothers were not incentivized to stop nursing their infants in order to participate. During the protocol development phase for this PMR, the Division will involve the Pediatric Ethics consultants and the Maternal Health Staff in the review of the proposed protocol.

Pediatric patients ages ≥2 years. The clinical trial information for this age group will be included in Section 14 Clinical Studies and Section 6 Adverse Reactions. Efficacy and safety will be addressed in Section 8.4, referring readers to Sections 6 and 14. In addition, pharmacokinetic information for this age group will be included in Section 12.3 Pharmacokinetics. The Clinical Pharmacology review notes that serum levels of intact glycerol phenylbutyrate were not evaluated in UCD patients less than age 6 years. In the PMR study, this will be assessed.

PMRs. The approval letter will state the following regarding the PMRs that will be required under FDAAA, and lists the following PMR trials:

> We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of neurologic toxicity related to the use of Ravicti (glycerol phenylbutyrate) in pediatric patients and in treatment-naïve patients, and as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate), and to assess a signal of a serious risk of carcinogenicity as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate).
>
> Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of neurologic toxicity related to the use of Ravicti (glycerol phenylbutyrate) in pediatric patients and in treatment-naïve patients, and as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate), and to assess a signal of a serious risk of carcinogenicity as a result of exposure through breast milk in infants whose mothers are treated with Ravicti (glycerol phenylbutyrate).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2013-1 A clinical trial to assess the safety, efficacy, and pharmacokinetics of Ravicti (glycerol phenylbutyrate) and its metabolites (PBA, PAA and PAGN) during Ravicti (glycerol phenylbutyrate) treatment in pediatric patients with Urea Cycle Disorders who are under 2 months of age.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	August 2013
Trial Completion:	August 2017
Final Report Submission:	March 2018

2013-2 A clinical trial to assess the safety, efficacy, and pharmacokinetics of Ravicti (glycerol phenylbutyrate) and its metabolites (PBA, PAA and PAGN) during Ravicti (glycerol phenylbutyrate) treatment in pediatric patients with Urea Cycle Disorders who are ages 2 months to less than 2 years.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	July 2013
Trial Completion:	July 2016
Final Report Submission:	December 2016

2013-3 A milk-only lactation trial in lactating female patients with Urea Cycle Disorders receiving Ravicti (glycerol phenylbutyrate) to assess the pharmacokinetics of Ravicti (glycerol phenylbutyrate) and its active metabolites in breast milk using an assay that has been validated in milk.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2013
Trial Completion:	June 2015
Final Report Submission:	December 2015

2013-4 A randomized, controlled clinical trial to assess the safety and efficacy of Ravicti (glycerol phenylbutyrate) in patients with Urea Cycle Disorders who are treatment naïve to phenylbutyrate.

The timetable you submitted on January 30, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	August 2013
Trial Completion:	June 2016
Final Report Submission:	March 2017

9. Other Relevant Regulatory Issues

Both the Clinical Reviewer and CDTL have reviewed the financial disclosure information submitted by the applicant in this NDA. They did not identify an investigator with a proprietary interest that could have affected the outcome of any study.

The DSI reviewer found that the data from the 3 sites selected for inspection were reliable and could be used in support of the NDA.

10. Labeling

See other Sections of this review for discussion of key labeling review issues. Expert reviewers from OSE, Pediatric and Maternal Health Staff and the Office of Pediatric Therapeutics were consulted to address specific review issues that impacted pediatric labeling (including the Contraindication for infants less than 2 months of age), pregnancy labeling, and the Nursing mothers section.

The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name, Ravicti, was acceptable as of November 29, 2012.

The Thorough QT team recommended language for the description of the QT study in the Pharmacodynamic section of the label.

The Medication Guide and labeling were revised in response to OPDP concerns regarding the proposed name of the registry website, which was promotional in tone. In addition, I removed (b) (4) from the list of serious side effects of Ravicti in the Medication Guide, because this item in Warnings refers to the impact of these

conditions (that the patient already has, not due to Ravicti) on the absorption of Ravicti. This Warning is not a "side effect" and its inclusion as a side effect would cause confusion.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment
  All disciplines have recommended approval and I concur that the risk/benefit of Ravicti is favorable. Phenylbutyrate has been marketed for decades and this provides a product source of phenylbutyrate that does not contain as much sodium as the currently marketed product. It is purported to be more palatable; however, data to support that were not submitted and reviewed. The risks associated with phenylbutyrate are very familiar to the specialists who use this nitrogen scavenging therapy to manage ammonia in their patients with urea cycle disorders. Hyperammonemia can be life threatening, and there are few nitrogen scavenging products approved. New information regarding the carcinogenicity of phenylbutyrate were provided in this application, and the product labeling will clearly describe this potential risk. Remaining knowledge gaps regarding dosing in pediatric subpopulations will be addressed with PMRs under FDAAA. A PMR will investigate whether Ravicti and/or its metabolites enter breast milk, which is important information for nursing mothers, since the product is carcinogenic and its active metabolite is known to be associated with neurotoxicity. A PMR trial will be conducted to further characterize the safety and efficacy of initiating treatment with Ravicti in treatment naïve patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The Medication Guide in the product labeling is a non-REMS Medication Guide.

- Recommendation for other Postmarketing Requirements and Commitments
  See Sections 6 and 8 above, as well as the Approval letter for details regarding the PMR trials, which will be required under FDAAA. In addition, there will be a PMC to conduct a drug interaction study.

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/s/

DONNA J GRIEBEL
02/01/2013