15 November 2018
EMA/CHMP/831384/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RAVICTI

International non-proprietary name: glycerol phenylbutyrate

Procedure No. EMEA/H/C/003822/II/0019

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Explanation
µg	microgram
µmol	micromole
AA	amino acid
ADRs	adverse drug reactions
AE	adverse event
ALT	alanine aminotransferase
AMMONAPS	European tradename for sodium phenylbutyrate
AMMONUL	sodium phenylacetate and sodium benzoate
ANOVA	analysis of variance
ARG	arginase
ASS	argininosuccinate synthetase
ASL	argininosuccinate lyase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration versus time curve
AUC0-24	AUC from time 0 (predose) to 24 h
BA	bioavailability
BE	bioequivalence
BID	twice daily
BRIEF	Behavior Rating Inventory of Executive Function
BSA	body surface area
BUPHENYL	United States tradename for sodium phenylbutyrate
CBCL	Child Behavior Checklist
CFR	Code of Federal Regulations
CHMP	committee for medicinal products for human use
CI	confidence interval
CITRIN	aspartate glutamate transporter deficiency; also referred to as Citrullinemia II
CL/F	apparent clearance
CLIF	apparent oral clearance
Cmax	maximum plasma concentration
Cmax-ss	maximum plasma concentration at steady state
Cmin	minimum plasma concentration
CPS	carbamyl phosphate synthetase
CSR	clinical study report
CYP	cytochrome P450
ECG	electrocardiogram
e.g.	for example
EMA	European Medicines Agency
EU	European Union
EOP2	end of phase 2
FDA	Food and Drug Administration
Fe	fraction excreted in urine
GCP	good clinical practices
GPB	glycerol phenylbutyrate
GT4P	glycerol tri-(4-phenylbutyrate) (now referred to as glycerol phenylbutyrate)
GT4P-F	80% formulation of glyceryl tri-(4-phenylbutyrate)
h	hour
HAC	hyperammonaemic crises
HE	hepatic encephalopathy
HHH	hyperornithinemia–hyperammonaemia–homocitrullinuria (HHH syndrome); also referred to as ornithine translocase deficiency
HPN 100	glycerol phenylbutyrate, formerly glyceryl tri (4 phenylbutyrate)
ICH	international conference on harmonization
i.e.	that is
IND	investigational new drug
IQ	intelligence quotient
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent to treat
Ki	inhibition constant
LOQ	limit of quantification

Term	Explanation
LSM	least squares mean
MAA	Market Authorization Application
mL	milliliter
NAGS	N-acetylglutamate synthase
NaPAA	sodium phenylacetate
NaPBA	sodium phenylbutyrate
NDA	new drug application
ODD	orphan drug designation
OLFS	open-label fixed-sequence
OTC	ornithine transcarbamylase
PAA	phenylacetate/phenylacetic acid
PAGN	phenylacetylglutamine
PBA	(formerly 4-)phenylbutyrate/(formerly 4-)phenylbutyric acid
PD	pharmacodynamic
PDCO	EMA paediatric committee
PIP	paediatric investigational plan
PK	pharmacokinetic
PopPK	population pharmacokinetics
PREA	paediatric research development act
QT	electrocardiographic interval from beginning of the QRS complex to end of the T wave
QTc	time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RAVICTI	EU trade name of medicinal product interchangeable with HPN-100/glycerol phenylbutyrate
SAE	serious adverse event
SAP	scientific advisory panel
SAP	statistical analysis plan
SD	standard deviation
SE	safety extension
SE	standard error
SmPC	summary of product characteristics
SO	switch over
SOC	system organ class
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TID	three times daily
UCD	urea cycle disorder
ULN	upper limit of normal
U-PAGN	urinary PAGN
U-PAGN0-24	urinary phenylacetylglutamine excreted from 0–24 h
US	United States
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Horizon Pharma Ireland Limited submitted to the European Medicines Agency on 14 February 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 - Extension of indication to include in the authorised indication the new paediatric population from 0 to 2 months for RAVICTI based on the final results from study HPN-100-009, an Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate in Paediatric Subjects under Two Years of Age with Urea Cycle Disorders (UCDs); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

This submission covers as well the requirement to submit clinical studies in the paediatric population in accordance with Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') for study HPN-100-009.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

RAVICTI, was designated as an orphan medicinal product EU/1/15/1062 on 1 December 2015. RAVICTI was designated as an orphan medicinal product in the following indication:

RAVICTI is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) 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).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0068/2014 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0191/2018.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Jayne Crowe

Timetable	Actual dates
Submission date	14 February 2018
Start of procedure:	23 June 2018
Rapporteur's preliminary assessment report circulated on:	27 July 2018
CoRapporteur's preliminary assessment report circulated on:	17 August 2018
CHMP members comments	10 September 2018
Joint Rapporteur's updated assessment report on circulated on:	13 September 2018
CHMP Rapporteur Assessment Report	31 October 2018
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2018
MAH's responses submitted to the CHMP on:	15 October 2018
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	31 October 2018
CHMP comments	5 November 2018
CHMP opinion:	15 November 2018

2. Scientific discussion

2.1. Introduction

Ravicti is indicated in the EU for use as a nitrogen-binding agent for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate-synthase-I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency

hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Ravicti (HPN-100) is a prodrug of phenylbutyric acid (PBA). PBA is converted via β-oxidation to its active metabolite phenylacetic acid (PAA), which is conjugated with glutamine to form phenylacetylglutamine (PAGN), which mediates waste nitrogen removal through urinary excretion.

The initial application (licensed in February 2016) included a comprehensive analysis of clinical safety and efficacy information on Ravicti from 12 controlled and uncontrolled clinical studies.

With this application the MAH has submitted the final clinical study report of the clinical trial HPN-100-009 to support to extend the use of Ravicti to the specific subset 0 to 2 months of the paediatric population.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The applicant submitted a justification for not providing an updated environmental risk assessment that the variation to extend the therapeutic indication for use of RAVICTI in the neonate to 2 months old paediatric population does not significantly change the exposure, overall risk and conclusions from the ERA performed in 2015 at the moment of granting the MA for Ravicti, since the expected number of additional patients in the EU Member States is overall low and patients in the neonate to 2 months age group will be treated on very low daily doses.

The justification for not providing an updated Environmental Risk Assessment was considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number	Phase	Study Design	Study Objective	Subject Status/Patient Diagnosis	Number Exposed to HPN-100/ Control(s)[a]
HPN-100-009	3	Non-randomized, open label study with a safety extension until subjects reached the age of 2 years or until they had received RAVICTI in the study for at least 6 months and were eligible for commercially available drug.	Safety and efficacy	Paediatric UCD (2 months to < 2 years of age)	10/-
				Paediatric UCD (newborns to <2 months of age)	16/-

HPN-100 = glycerol phenylbutyrate; UCD = urea cycle disorder.

2.3.2. Pharmacokinetics

The pharmacokinetics of HPN-100 were evaluated in paediatric subjects 0 -2 months with either a diagnosed or clinically suspected UCD including all UCD subtypes, except N-acetyl glutamate synthetase (NAGS) deficiency in study HPN 100 009 (for details of the studies referred in this section, please see section 2.4 Clinical efficacy).

Serial and single blood samples were collected for PK analysis of plasma PBA, PAA, and PAGN; and serial and single urine samples were collected for PK analysis of urinary PAA, PAGN, and creatinine. Parameters, such as maximum observed plasma concentration (Cmax), minimum observed plasma concentration (Cmin), average plasma concentration (Cavg), AUC from time 0 to time of last measurable plasma concentration (AUC0-last) on the first day of Ravicti alone dosing, and time to maximum concentration (Tmax) were characterized.

If appropriate, additional PK parameters, such as apparent clearance, may have been characterized via a population PK approach as data permitted.

All 16 subjects in the birth to <2 months' cohort were included in the PK analysis set. The dosage of RAVICTI was individualized according to treating physicians' judgement. The median dose was 8.36 ml/m2/day and ranged from 1.0 mL to 3.9 mL per day (4.0 mL/m2/day to 15.6 mL/m2/day) during transition (day 1 to 7).

PK results were also presented in a second cohort of 10 patients, aged between 2 months and 2yrs. The median dose of Ravicti on Day 1 in these patients was 8.9 mL/m2/day (9.79 g/m2/day). Pharmacokinetic analysis for both patient groups are summarised in **Table 1**.

Table 1. Summary of Pharmacokinetic Parameters for PBA, PAA and PAGN on First Full Day of Ravicti Dosing, Study HPN-100-009

Birth to <2 months cohort Study HPN-100-009 N=16					**2 months to < 2 years cohort N=10**			
	PBA	**PAA**	**PAGN**	**PAA/PAGN**	**PBA**	**PAA**	**PAGN**	**PAA/PAGN**
AUC 0-last µg*h/mL mean	374.5 ±390.5	1321.2 ±1220.5	1384.1 ±1141		280.9 ±293.6	246.1 ±238.6	583.8 ±285.2	
Cmax	46.2	115.3	102.1		42.44	36.52 ±31.784	62.5 ±27.281	

µg/mL **mean**	±49.8	±102.0	±48.6		±36.715			
Cavg µg/mL **mean**	23.15 ±23.04	86.96 ±100.28	79.97 ±47.33		21.5 ±21.6	18.3 ±17.5	44.0 ±18.9	
PAA/PAGN Cmax ratio **mean**				1.37 (median 0.99; range 0.14 to 4.94)				0.5 (median 0.41; range 0.08 to 1.17)

Age <1 month Cohort subgroup (n=10)

Exposure to PBA in terms of Cavg (±SD) was 22.91 ±27.65 µg/mL. ±1.56. Mean PAA and PAGN concentrations were 123.17 ±112.38 µg/mL and 96.15 ±50.96 µg/mL respectively. The PAA/PAGN Cmax ratio was 1.75

Age 1 to <2 months subgroup (n=6)

Exposure to PBA in terms of Cavg was 21.5±21.6 µg/mL. Cavg of PAA was 26.60±20.91 µg/mL; Mean Cavg for PAGN was 52.98 ±25.46 µg/mL. The PAA/PAGN Cmax ratio was 0.74 ± 0.47. The PAGN concentrations in urine ranged from 166 µg/mL to 14,500 µg/mL on the first full day of Ravicti treatment.

PAA and PAGN concentrations in urine

Children age 0 - <2 months old

Urine PAA and PAGN samples were collected pre-dose and post-dose at 0.5-1.5, 1.5-2.5, 4-6, 7.5-8.5, and 12-24 hour intervals. PAGN concentrations in urine ranged from 166 µg/mL to 14,500 µg/mL on the first full day of Ravicti treatment, indicating intestinal hydrolysis of Ravicti. Additional sampling was done on Day 7, Months 1-3, and Month 6, followed by every 3 months until subjects completed or prematurely terminated the study. Longitudinal plots indicated no accumulation of urine PAA during the entire course of the study but showed a general increase in urine PAGN excretion in some subjects over time.

Children age 2 months to 2 years cohort

PAA concentrations in urine ranged from 1.05 µg/mL to 50.3 µg/mL on the first full day of Ravicti treatment. PAGN concentrations in urine ranged from 140 µg/mL to 24600 µg/mL.

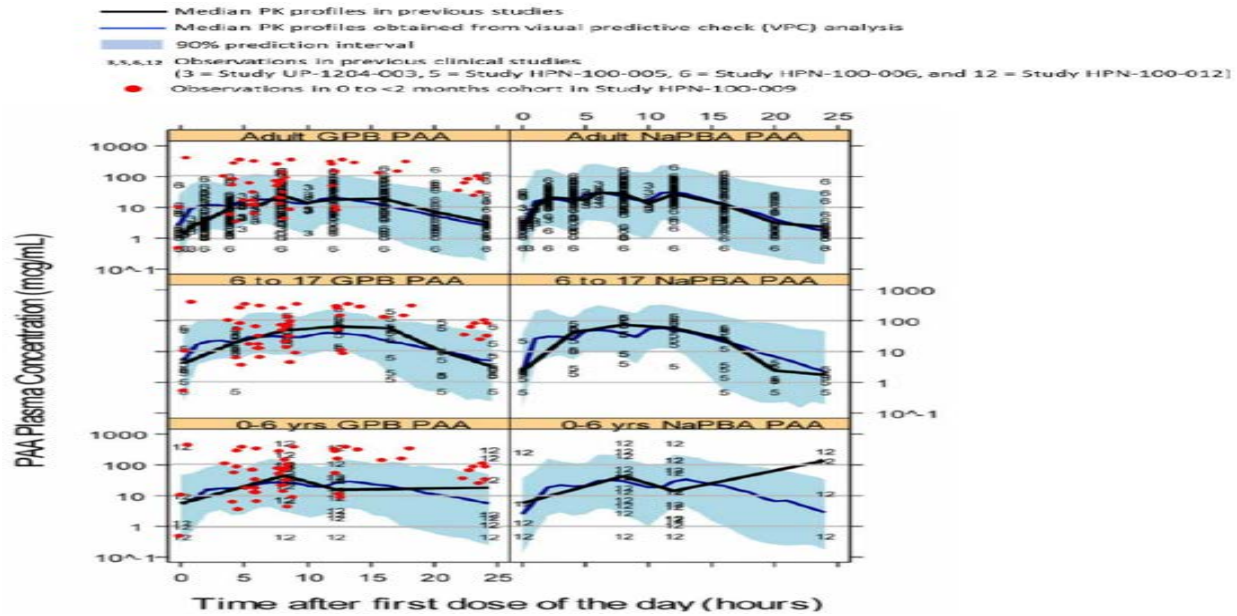
Safety extension period

PK samples were collected during the safety extension phase on Day 7, Months 1-3, Month 6, and every 3 months until subjects completed or prematurely terminated the study. Plasma PBA, PAA and PAGN concentrations during the safety extension period were plotted by subject. The plasma concentrations of the 3 Ravicti-associated analytes (PBA, PAA, and PAGN) for both age cohorts (0-<2 months and 2months< 2years) were stable during the safety extension period. No evidence of accumulation was observed (data not shown). Most subjects had plasma PAA/PAGN ratios less than 1 throughout the study indicating that no saturation of the conjugation of PAA with glutamine to form PAGN was evident.

PK data comparison with results in older children or adults

The concentration-time data observed in Study HPN-100-009 were plotted against the PK profiles observed in older children and adults (Studies HPN-100-005, HPN-100-006, HPN-100-012 and UP 1204-003, which have been evaluated during the initial marketing authorisation of Ravicti). **Figure 1** shows the results for PAA.

Figure 1. Observed plasma PAA concentrations in Study HPN-100-009 overlaid with observations from previous studies



PAA concentrations were within or higher than the 90% PI in adults and the 6-17 year age cohort from Studies HPN-100-005, HPN-100-006, and HPN-100-012 and UP 1204- 003.4,5. The PAA exposure levels, however, were within the range of the 0 to 6 year old cohort.

The PAGN concentrations were within or slightly higher than the 90% PI in adults from Studies HPN-100-005, HPN-100-006 and UP 1204-003.

Most of the PBA concentrations in the 0 to <1 month and 1 to <2 month cohorts were within or below the 90% prediction interval (PI) in previous studies.

Correlation of covariates with Ravicti analytes exposure

A population PK analysis was conducted to identify if body size metrics or other covariates could predict some of the variability in Ravicti exposure in the target age group with UCDs. This analysis utilised individual baseline covariate demographic information including, total body weight, age, height, sex, race, ethnicity and body surface area.

Graphical visualisation showed that most of the plasma concentrations of PBA, PAA, and PAGN in the infants were within or below the 90% prediction interval in previous studies in older patients, although inter-individual variability was high.

In this model, the AUC last of plasma PAA moderately correlated with age ($R2=0.34$). There was a weak negative association between Cavg of PAGN and body weight and BSA ($R2>0.2$)). The two body size metrics, body weight and BSA, did not show a significant difference in their association with PAA and PAGN exposure.

2.3.3. Discussion on clinical pharmacology

PK data from a total of 16 paediatric subjects in the target age group (0 to <2 months old) and 10 paediatric subjects in the 2 months<2yrs target age group were included in the PK evaluation.

Mean systemic PBA exposure did not differ significantly between the two cohorts. Plasma concentrations and AUC of PBA were in the same range in subjects with UCDs aged 0 to<2 months as those observed 2 months to 2 yrs which suggests comparable ability to break down Ravicti.

However, PAA and PAGN exposures were generally higher among patients <2 months of age compared with patient's ages >2 months. Blood levels of PAA can vary widely over the course of the day so samples collected randomly can be difficult to interpret. In that context a recommendation to further monitor PAA levels in patients aged 0-2 months was not considered useful.

However, as the rate of PAA metabolism to PAGN does correlate with BSA, as further illustrated in the higher PAA/PAGN Cmax mean ratio 1.37 (median 0.99; range 0.14 to 4.94) in the 0<2month cohort compared to the 0.5 mean ratio in the 2 months to <2 yrs. cohort. (Range 0.08 to 1.17 and a median of 0.41), the product information was updated to include PK data from the 16 paediatric subjects in the target age group (0 to <2 months old) and 10 paediatric subjects in the 2 months <2yrs target age group.

Subgroup analysis in patients aged ‹1 month and between 1 and 2 months did not reveal any differences between the two groups.

Some variability in analyte concentrations in both cohorts was observed but the variation in sampling time intervals and the wide range of doses used could have contributed to inter individual fluctuation in PAA, PBA and PAGN.

The concentration-time data observed in Study HPN-100-009 when plotted against the PK profiles observed in older children and adults (from previously conducted studies). Most of the PBA concentrations in the age <1 month and age 1 to <2 months groups were within or below the 90% prediction interval (PI). The PAA concentrations were within or higher than the 90% PI in adults and the age 6-17 year cohort from Studies HPN-100-005, HPN-100-006, HPN-100-012, and UP 1204-003, and comparable to the age 0-6 year cohort from Studies HPN-100-005, HPN- 100-006, and UP 1204-003. The PAGN concentrations were within or slightly higher than the 90% PI in adults.

Overall these data show that pharmacokinetics of RAVICTI in children under 2 months of age are largely similar to those of the other age groups.

Evaluation of long-term exposure in the 0-<2month age group indicated that the plasma concentrations of PBA, PAA and PAGN did fluctuate somewhat during the safety extension phase but were generally stable with no clear signs of accumulation. There was a trend towards increased urinary PAGN in this age cohort. The ratio of PAA/PAGN showed a large inter-patient variability.

Comparable correlations of PBA and PAGN clearance with body weight and BSA provide support for the use of dosing in subjects 0 to <2 months old with UCDs based on both body-size metrics.

2.3.4. Conclusions on clinical pharmacology

The overall PK profile is broadly similar between the 0 to <2-month age group the PK profiles observed in older children and adults. Overall the clinical pharmacology of glycerol phenylbutyrate is considered to have been adequately characterised from the submitted data in the paediatric population up to 2-months of age.

2.4. Clinical efficacy

2.4.1. Main study

Study HPN-100-009: An open label study of the safety, efficacy and pharmacokinetics of glycerol phenylbutyrate (GPB; RAVICTI) in Paediatric Subjects under two years of age with urea cycle disorders (UCDs)

Methods

After enrolment, initiation or transition of treatment to Ravicti occurred from Day 1 to Day 4. Subjects were transitioned to Ravicti and monitored over a period of approximately 24 hours. Subjects presenting with a hyperammonaemic crisis did not initiate Ravicti until after their blood ammonia level was below 100 µmol/L while receiving AMMONUL (combination of sodium benzoate [NaBz] and sodium phenylacetate [NaPAA]) and/or undergoing haemodialysis. Following transition, subjects underwent continued ammonia monitoring for 24 to 72 hours depending on their age, condition, and course. The transition period was followed by a safety extension period where subjects received Ravicti until they reached the age of 2 years or until they had received Ravicti in the study for at least 6 months and were eligible for commercially available drug.

Study participants

Inclusion criteria

- Male and female subjects up to 2 years of age
- Signed informed consent by subject's parent/legal guardian
- UCD diagnosis or suspected diagnosis of any subtype, except NAGS deficiency. If UCD had not been previously confirmed by genetic testing, consent was obtained from parent/legal guardian to perform genetic testing. Genetic testing for UCD diagnosis confirmation could have occurred after enrolment but must have been within 60 days of baseline. The results of the testing were made available to parents/legal guardians per institutional practices, including the availability of genetic counselling. If genetic testing was inconsistent with or excluded a UCD diagnosis, the subject was withdrawn from the study.

NOTE: A UCD diagnosis was suspected when a subject experienced a hyperammonaemic event with ammonia level >100 µmol/L accompanied by signs and symptoms compatible with hyperammonemia in the absence of other obvious causes

Exclusion Criteria

- Use of any investigational drug within 30 days prior to Day 1
- Uncontrolled infection (viral or bacterial) or any other condition known to precipitate hyperammonemic crises. Once these precipitating factors were medically controlled, subjects presenting in crisis were eligible.
- Any clinical or laboratory abnormality of Grade 3 or greater severity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, except Grade 3 elevations in ammonia and liver enzymes, defined as levels 5 to 20 times the upper limit of normal (ULN) in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyltransferase (GGT) in a clinically stable subject
- Any clinical or laboratory abnormality or medical condition that, at the discretion of the Investigator, may have put the subject at increased risk by participating in this study

- Known hypersensitivity to PAA or PBA
- Liver transplantation, including hepatocellular transplant
- Subjects on hemodialysis at time of initiating RAVICTI
- Subjects on RAVICTI for UCD management

Treatments

Subjects enrolled in the study received Ravicti Oral Liquid, administered orally, 3-6 times per day depending on the feeding schedule and at the discretion of the Investigator. The starting dose of Ravicti was based on UCD status (newly diagnosed or already stable on NaPBA and/or NaBz) and whether a hyperammonemic crisis was present.

Subsequently, the dose could have been adjusted at the discretion of the Investigator and according to the needs of each subject and accounting for the subject's expected level of growth and development, BSA, ammonia control, and blood and urinary metabolite levels. The total daily dose should not have exceeded 17.5 mL.

Objectives

The objectives of this study were to assess safety, ammonia control, and PK of Ravicti for the treatment of paediatric subjects up to 2 years of age with UCDs.

Outcomes/endpoints

Efficacy was assessed by the successful transition to Ravicti with controlled ammonia (defined as no clinical symptoms of hyperammonaemia and ammonia <100 µmol/L).

The Investigator made an assessment of clinical status at the end of the transition period and determined if successful transition to Ravicti occurred during the period.

Safety endpoints were rate of hyperammonaemic crises during the first 6 months on Ravicti; rate of treatment-emergent adverse events (TEAEs); amino acid panel; growth and development assessed as Z-scores for height (or length), head circumference, weight, body mass index (BMI), and body surface area (BSA), and changes over time.

Sample size

Approximately 26 subjects were to be enrolled, with at least 16 subjects from birth to <2 months of age (including at least 8 subjects from birth to <1 month of age and at least 3 subjects from 1 month to <2 months of age).

No formal sample size calculation was performed. The sample size was based on clinical and practical considerations rather than statistical considerations

Randomisation

Not applicable.

Blinding (masking)

This was an open-label study.

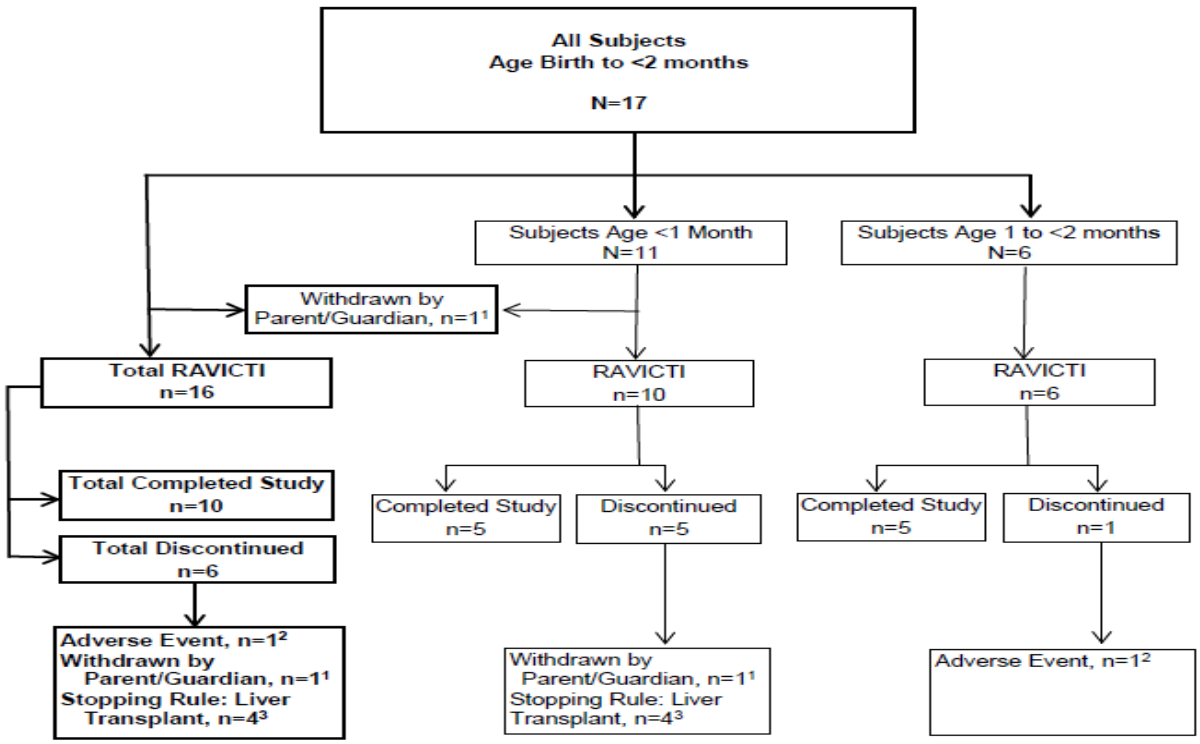
Statistical methods

Data were summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentages for categorical variables. No statistical testing was performed.

Age (days) was derived as Date of Screening Visit – Date of Birth. One month equalled 30 days when defining age categories. Unless otherwise specified, the baseline value for each variable was the last non-missing value recorded on the day of, but prior to the first dose of study drug treatment. If this value was not available, the last Screening value was used.

Results

Participant flow



Recruitment

Study initiation date: 31 December 2014

Study completion date: 17 July 2017 ((for study and for birth to <2 months age group)

Conduct of the study

Fifteen of the 17 subjects had 1 or more deviations. The most frequent deviations were isolated study procedures/assessment not done (e.g., temperature, height, weight, or blood pressure not measured; PK samples not collected) and visits conducted outside the protocol-specified time window. No subjects were withdrawn from the study because of a protocol deviation.

Baseline data

Demographic and other baseline characteristics for the 16 subjects in the age birth to <2 months

cohort who received study drug (Safety population) are summarized in **Table 2**.

Table 2. Demographic and Baseline Characteristics (Safety Population, Study HPN-100-009)

		Age <1 mos (N=10)	Age 1 mos to <2 mos (N=6)	Total 0 to <2 mos (N=16)
Age (months)[1]	n	10	6	16
	Mean (SD)	0.33 (0.196)	1.66 (0.203)	0.83 (0.697)
	Median	0.30	1.69	0.48
	Min, Max	0.1, 0.7	1.3, 2.0	0.1, 2.0
Sex	Male	7 (70.0%)	2 (33.3%)	9 (56.3%)
	Female	3 (30.0%)	4 (66.7%)	7 (43.8%)
Ethnicity	Hispanic or Latino	1 (10.0%)	0	1 (6.3%)
	Not Hispanic or Latino	9 (90.0%)	6 (100.0%)	15 (93.8%)
Race	American Indian or Alaska Native	0	0	0
	Asian	1 (10.0%)	1 (16.7%)	2 (12.5%)
	Black or African-American	1 (10.0%)	0	1 (6.3%)
	Native Hawaiian or other Pacific Islander	0	0	0
	White	8 (80.0%)	4 (66.7%)	12 (75.0%)
	Other[2]	0	1 (16.7%)	1 (6.3%)
Average Height (cm)[3]	n	10	6	16
	Mean (SD)	51.05 (3.967)	55.77 (5.537)	52.82 (5.022)
	Median	50.25	53.15	52.00
	Min, Max	45.0, 58.0	51.9, 66.0	45.0, 66.0
Average Weight (kg)[3]	n	10	6	16
	Mean (SD)	3.54 (0.419)	4.54 (0.622)	3.92 (0.696)
	Median	3.58	4.50	3.87
	Min, Max	2.9, 4.0	3.8, 5.5	2.9, 5.5
Baseline BMI (kg/m^2)[4]	n	10	6	16
	Mean (SD)	13.67 (1.690)	14.65 (1.251)	14.04 (1.573)
	Median	14.13	14.65	14.38
	Min, Max	10.2, 15.8	12.6, 16.2	10.2, 16.2
Average Head Circumference (cm)[3]	n	10	6	16
	Mean (SD)	35.01 (1.178)	37.64 (1.709)	36.00 (1.881)
	Median	35.13	37.38	35.93
	Min, Max	33.0, 36.5	35.9, 40.8	33.0, 40.8
BSA (m^2)	n	10	6	16
	Mean (SD)	0.22 (0.020)	0.26 (0.033)	0.24 (0.032)
	Median	0.22	0.26	0.24
	Min, Max	0.2, 0.3	0.2, 0.3	0.2, 0.3

1 Age was calculated as the rounded down integer value in months of [(Date of Screening Visit – Date of Birth)/30.4375].
2 Other = biracial - white and black
3 Height (length), weight, and head circumference were measured twice at each scheduled assessment, and an average was calculated.
4 BMI was based on the average weight and average height.

BMI = body mass index; BSA = body surface area; Max = maximum; Min = minimum; mos = month; SD = standard deviation.

Numbers analysed

A total of 27 paediatric subjects over 2 age cohorts were recruited. Sixteen of the subjects enrolled in the age birth to <2 months cohort received study drug and were therefore included in the Safety population, which was used for the analysis of efficacy and safety.

All of these 16 subjects who received study drug had individual concentration-time profiles that allowed computation of meaningful PK parameter values and were included in the PK Evaluable population.

Age refers to subject age at study enrolment.

Outcomes and estimation

Successful Transition to Ravicti with Controlled Ammonia

Regardless of their treatment status at study entry or age (<1 month or 1 month to <2 months), all 16 subjects (100.0%) achieved successful transition to study drug with controlled ammonia (i.e., no clinical symptoms of hyperammonaemia and ammonia <100 µmol/L). Most subjects achieved successful transition by the end of 1 day of receiving Ravicti alone, and all subjects achieved successful transition by the end of 3 days of receiving Ravicti alone. Although 3 subjects had Day 7 ammonia values of 106, 119, and 127 µmol/L, none had associated signs and symptoms of hyperammonaemia.

Controlled ammonia continued in the safety extension period for the majority of subjects. The overall percentage of treated subjects age birth to <2 months with controlled ammonia and no clinical symptoms suggestive of a hyperammonaemic crisis ranged from 8/14 (57.1%) to 3/4 (75.0%) at the Month 1 4, 9, and 15 visits and from 8/9 (88.9%) to 10/10 (100.0%) at the remaining visits.

Compared to baseline (the 7-day period prior to Day 1) in subjects age birth to <2 months, there was a median decrease in normalized ammonia level at each post-baseline visit in the transition period and majority of visits in the safety extension period. There was a mean decrease from baseline at all visits in both study periods.

Age <1 month subgroup

For subjects age <1 month, there was a median (and mean) decrease from baseline at most post-baseline visits. For subjects age 1 month to the percentage of subjects with controlled ammonia ranged from 4/9 (44.4%) to 5/7 (71.4%) at Months 1-4 and 4/5 (80.0%) to 5/5 (100.0%) at the other visits.

Age 1 month to <2 months subgroup

The percentage with controlled ammonia ranged from 1/3 (33.3%) to 4/6 (66.7%) at Months 1, 3, 4, 9, and 15 and 4/5 (80.0%) to 6/6 (100.0%) at the other visits. No differences between age groups or differences based on status at study entry were apparent.

Ammonia Assessments

The median baseline normalized ammonia (the 7-day period prior to Day 1 study drug dosing) was 52.4 µmol/L (mean [±SD] 94.3 ±139.28 µmol/L, range 15 to 600 µmol/L).

During the transition period, the median change from baseline ranged from -7.4 µmol/L to -1.0 µmol/L. At the end of the transition period, the median change from baseline was -2.9 µmol/L.

During the safety extension period, the median change from baseline at Months 1-6, 9, and 24/End of Treatment (EOT) (n=8 to 15 subjects) ranged from -7.7 µmol/L to 5.0 µmol/L. At Months 12, 15, and 18

(n=3 to 6 subjects), the median change ranged from -27.4 µmol/L to 7.0 µmol/L. At 24 months the median change from baseline was 2.4 µmol/L.

Age <1 month subset

For subjects age <1 month, the median baseline normalized ammonia was 49.5 µmol/L (mean [±SD] 108.9 ±174.7 µmol/L, range 15 to 600 µmol/L). During the transition period, the median change from baseline ranged from -7.5 µmol/L to -23.4 µmol/L. At the end of the transition period, the median change from baseline was -12.5 µmol/L.

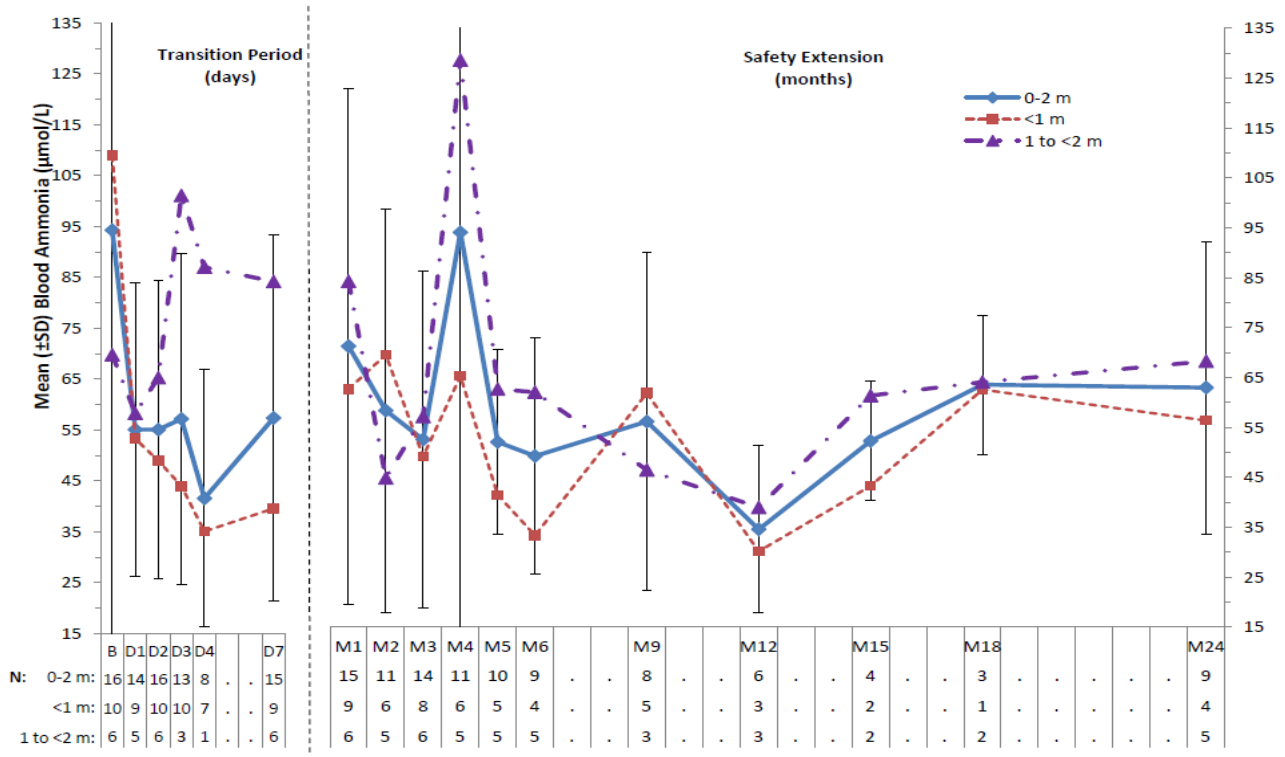
During the safety extension period, the median change from baseline ranged from -7 µmol/L (month 9 n=5) to -35.8 µmol/L (month 18 n=1). At 24 months the median change from baseline was -13.5 µmol/L.

Age 1 month to <2 months subset

The median baseline normalized ammonia was 56.1 µmol/L (mean [±SD] 69.8 ±46.22 µmol/L, range 42 to 163 µmol/L). During the transition period, the median change from baseline ranged from -2.1 µmol/L (mean [±SD] -13.7 ±25.4 µmol/L,) to 45.0 µmol/L mean 44.2[±SD] ±11.50. At the end of the transition period, the median change from baseline was -1.0 µmol/L. During the safety extension period, the median change from baseline ranged from 19 µmol/L (mean [±SD] 53.2 ±175.90) (month 4 n=5) to - 19.2 µmol/L (mean [±SD] -48.7 ±71.22) (month 12 n=3). There was a median increase from baseline at the majority of study visits, a mean increase from baseline for the majority of visits in the transition period, and a mean decrease from baseline for the majority of visits in the safety extension period. At 24 months the median change from baseline was 28.5µmol/L. (Mean ±SD -3.8 ±SD 78.01)

Mean levels off ammonia over time are shown in **Figure 2**.

Figure 2. Mean (±SD) Normalized Ammonia Levels over Time (Safety Population) 0 to <2 months Age Group, Study HPN-100-009



Source: Table 14.2.2b
Error bars = SD for 0-2 months population. SDs not fully shown: 139.28 (B) and 106.45 (M4).
M24 = Month 24 or End of Treatment if prior to Month 24.
B = baseline; D = day; M (or m) = month; N = number of subjects; SD = standard deviation.

Ancillary analyses

The study included a further 11 patients, aged between 2 months and 2 years, and results from this group of patients is presented in this section.

Successful Transition to Ravicti with Controlled Ammonia

Prior to the start of study drug, 7 subjects were stable on NaPBA and/or NaBz, 2 subjects were newly diagnosed and not in hyperammonaemic crisis, and 1 subject was in hyperammonaemic crisis and receiving AMMONUL. Regardless of their status at study entry, all 10 subjects (100.0%) achieved successful transition to study drug by the end of 2 days of receiving Ravicti alone, with controlled ammonia (i.e., no clinical symptoms of hyperammonaemia and ammonia <100 µmol/L). At the Month 1-9 visits, the percentage ranged from 5/7 (71.4%) to 7/8 (87.5%). At the Month 12, 15, 18, and 24 visits, the percentage ranged from 1/1 (100.0%) to 4/4 (100.0%).

Ammonia Assessments

The median baseline normalized ammonia (the 7-day period prior to Day 1 study drug dosing) was 67.2 µmol/L (mean [±SD] 96.8 ±76.86 µmol/L, range 27 to 287 µmol/L). During the transition period there was a mean decrease from baseline at each visit. On Days 1, 2, and 7, the median change from baseline ranged from -16.9 µmol/L (mean [±SD] -41.5 ±79.35) to -6.0 µmol/L (mean [±SD] -32.0 ±59.13).

At the end of the transition period, the median change from baseline was -9.2 µmol/L (mean -38.6 ± 70.69). During the safety extension period, the median change from baseline at Months 1-6 (n=6 to 9 subjects) ranged from -39.3 µmol/L (mean [±SD] -34.9 ±148.80) to 8.1 µmol/L (mean [±SD] -12.7 ±90.70). At Months 9-24 (n=1 to 4 subjects), the median change ranged from -238.7 µmol/L (n=1) to -8.1 µmol/L (mean [±SD] -68.8 ± 126.04). At 24 months the median change from baseline was -8.1µmol/L (n=3).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

HPN-100-009 was an open label study involving children under-two years of age. Studies in UCD are difficult to conduct due to the small numbers of patients. The target population of very sick and very young infants presents with additional difficulties as it limits for example the availability of patients for blood sampling. Rigorous evaluation of the clinical benefit of Ravicti in the paediatric population would require a long term active-controlled study with clinical endpoints related to hyperammonaemia and its consequences. For ethical and logistical reasons such a study is not feasible.

Considering these difficulties, the open label study design with a transition period and long term extensions evaluating efficacy was considered acceptable.

Assessment of blood ammonia which was measured in this trial is central to the evaluation of efficacy and safety in UCDs, as it is the signature biochemical abnormality common to these disorders representing the surrogate for outcomes.

Efficacy data and additional analyses

Regardless of their status at study entry or age, all subjects achieved transition within 3 days. For patients in 0-<2months cohort controlled ammonia was achieved by most patients in the transition and safety extension periods and there did not appear to be a difference between age subgroups (<1 month vs. 1 month to <2 months) in terms of the proportions of patients achieving controlled ammonia.

For patients in 0-<2months cohort by the end of the transition period, the ammonia level was <100 µmol/ for all subjects. An increase in mean normalized ammonia levels was noted for the majority of visits in the transition period in the 1-<2month subgroup.

The percentage of subjects with controlled ammonia in the safety extension visits ranged from 57% to 100%. There was some fluctuation in mean normalized ammonia levels at each post-baseline visit in the extension period for this cohort. Mean normalized ammonia levels decreased overall at each post-baseline visit in the transition period and majority of visits in the safety extension period but there was a slight trend towards increased mean normalized ammonia levels with treatment for >1yr.

For the 2 months <2 years cohort mean normalized ammonia levels decreased at each post-baseline visit in the transition period and majority of visits in the safety extension period. The percentage of subjects with controlled ammonia ranged from 71% to 100%.

These efficacy study data demonstrate the therapeutic effectiveness of RAVICTI in children from birth to 2 months of age.

2.4.3. Conclusions on the clinical efficacy

Controlled ammonia levels were achieved in most paediatric patients up to 2 months of age with UCD, treated with glycerol phenylbutyrate. The effect size was comparable to that seen in older paediatric patients.

The CHMP concluded that the available clinical efficacy data were adequate to support the use of glycerol phenylbutyrate as an adjunctive therapy for the chronic management of patients from birth to two months of age with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

2.5. Clinical safety

Patient exposure

In the paediatric population in study HPN-100-009, safety analyses were conducted for the 16 treated subjects in the age birth to <2 months cohort and for each of the 10 subjects in the 2 months to <2 years cohort. Median duration on treatment for these subjects age was 9.97 months (mean [±SD] 10.67 ±6.142 months; range 1.9 to 20.4 months).

The median total daily dose was 8.36 mL/m2 by subject BSA (mean 8.39 ±2.680 mL/m2; range 4.0 to 15.6 mL/m2).

10 subjects age 2 months to <2 years received study drug the starting dose of study drug varied according to baseline UCD status (newly diagnosed, transitioning form NaPBA whether hyperammonaemic crisis was present), Doses ranged from 4.3 mL/m2/day to 11.2 mL/m2/day. The median total daily dose by subject BSA was 8.97 mL/m2 (mean 8.32 ±2.36 mL/m2). The median duration on treatment for the 10 subjects in this cohort was 4.68 months (mean±SD] 4.33 ±3.073 months; range 0.2 to 10.9 months).

Safety extension

During the safety extension period, 16 subjects aged between birth to <2 months received study drug. A total of 8 subjects (50.0%) received all planned doses during the safety extension. The median total daily dose by subject BSA was 8.10 mL/m2 (mean 7.97 ±2.240 mL/m2; range 3.1 to 12.7 mL/m2). Fifteen of the 16 subjects (93.8%) had at least 1 dose change in the safety extension period. The majority of the dose

changes were increases in the amount of study drug administered because of subject growth and/or elevated ammonia levels.

During the safety extension period, 9 subjects aged between 2 months and 2 years received study drug. The median total daily dose of study drug during the safety extension was 3.68 mL (mean 3.51 ±1.163 mL; range 1.7 to 5.7 mL). The median total daily dose by subject BSA was 8.21 mL/m2, or 9.03 g/m2. The median total daily dose by subject weight was 378.55 mg/kg. The median total daily study drug dose in grams was 4.05 g, and the median total daily PBA content administered was 3.76 g.

Of the 9 subjects who received study drug during the safety extension period, 7 subjects had at least 1 dose change. Almost all of the dose changes were increases in the amount of study drug administered because of subject growth or weight increase (4 subjects) and/or elevated ammonia levels (3 subjects).

Adverse events

Treatment-emergent Adverse Events **(**TEAEs) were defined as AEs with an onset date on or after the date of first dose of study medication until study discontinuation.

A total of 191 TEAEs were recorded in the age birth to <2 months cohort safety population. At least 1 TEAE was reported for each of the 16 (100.0%) subjects in the Safety population.

The SOCs most affected were Gastrointestinal disorders (14 [87.5%] subjects); Infections and infestations (13 [81.3%] subjects); Metabolism and nutrition disorders (10[62.5%] subjects); Skin and subcutaneous tissue disorders (9 [56.3%] subjects); Investigations and Respiratory, thoracic and mediastinal disorders (7 [43.8%] subjects each); and Blood and lymphatic system disorders 6 [37.5%] subjects).

The most frequently reported TEAEs by preferred term were dermatitis diaper, gastroesophageal reflux disease, hyperammonaemia, and vomiting (6 [37.5%] subjects each); diarrhoea, rash, and upper respiratory tract infection (5 [31.3%] subjects each); cough and nasopharyngitis (4 [25.0%] subjects each); anaemia, dehydration, ear infection, flatulence, teething, and urinary tract infection (3 [18.8%] subjects each); and constipation, hepatic enzyme increased, lethargy, metabolic acidosis, nasal congestion, neutropenia, oral candidiasis, oropharyngeal pain, plagiocephaly, pyrexia, respiratory syncytial virus infection, thrombocytopenia, and thrombocytosis (2 [12.5%] subjects each). No other TEAE was reported for more than 1 subject

TEAE Severity

Most of the TEAEs for subjects age birth to <2 months were Grade 1 (123 events) or Grade 2 (54 events). The most frequent Grade 3 TEAE was hyperammonaemia, which occurred in 3 (18.8%) subjects. Two of these subjects had 2 events of hyperammonaemia. Two of these subjects had 2 events of hyperammonaemia each, for a total of five Grade 3 events. The other Grade 3 TEAEs, occurring in 1 subject each, were anaemia; viral infection; weight decreased and lethargy (in the same subject); device related infection and medical device site infection (in the same subject); and meningitis bacterial, bacteraemia, and tracheitis (in the same subject). Of the Grade 3 TEAEs, anaemia, weight decreased, and lethargy were considered related to the study drug. These 3 TEAEs were non-serious; all other Grade 3 events were SAEs.

Discontinuation

One subject discontinued study drug because of a TEAE. This subject, who was 41 days old at study enrolment, was discontinued because of elevated liver enzymes.

TEAE Relationship to Study Drug

A total of 10 subjects age birth to <2 months had at least 1 study drug-related TEAE, for a total of 22 events and are summarised in **Table 3**.

Table 3. Study Drug-related treatment-emergent adverse events by System Organ Class, Preferred term. Safety Population, Study HPN-100-009

SOC[1] Preferred Term	Age <1 mos (N=10)	Age 1 mos to <2 mos (N=6)	Total 0 to <2 mos (N=16)
Total Number of Related TEAEs[2]	**11**	**11**	**22**
Number of Subjects with At Least 1 Related TEAE[2]	**5 (50.0%)**	**5 (83.3%)**	**10 (62.5%)**
Blood and lymphatic system disorders	**2 (20.0%)**	**0**	**2 (12.5%)**
Anaemia	1 (10.0%)	0	1 (6.3%)
Neutropenia	1 (10.0%)	0	1 (6.3%)
Thrombocytosis	1 (10.0%)	0	1 (6.3%)
Gastrointestinal disorders	**1 (10.0%)**	**2 (33.3%)**	**3 (18.8%)**
Diarrhoea	1 (10.0%)	1 (16.7%)	2 (12.5%)
Constipation	0	1 (16.7%)	1 (6.3%)
Flatulence	0	1 (16.7%)	1 (6.3%)
Gastrooesophageal reflux disease	0	1 (16.7%)	1 (6.3%)
Hepatobiliary disorders	**1 (10.0%)**	**0**	**1 (6.3%)**
Hepatic calcification	1 (10.0%)	0	1 (6.3%)
Investigations	**2 (20.0%)**	**2 (33.3%)**	**4 (25.0%)**
Amino acid level decreased	1 (10.0%)	0	1 (6.3%)
Blood bicarbonate decreased	1 (10.0%)	0	1 (6.3%)
Gamma-glutamyltransferase increased	1 (10.0%)	0	1 (6.3%)
Hepatic enzyme increased	0	1 (16.7%)	1 (6.3%)
Transaminases increased	0	1 (16.7%)	1 (6.3%)
Weight decreased	0	1 (16.7%)	1 (6.3%)
Metabolism and nutrition disorders	**0**	**1 (16.7%)**	**1 (6.3%)**
Hypophagia	0	1 (16.7%)	1 (6.3%)
Nervous system disorders	**0**	**1 (16.7%)**	**1 (6.3%)**
Lethargy	0	1 (16.7%)	1 (6.3%)
Tremor	0	1 (16.7%)	1 (6.3%)
Renal and urinary disorders	**1 (10.0%)**	**0**	**1 (6.3%)**
Nephrolithiasis	1 (10.0%)	0	1 (6.3%)
Skin and subcutaneous tissue disorders	**2 (20.0%)**	**1 (16.7%)**	**3 (18.8%)**
Rash	2 (20.0%)	1 (16.7%)	3 (18.8%)

Source: Table 14.3.2.3b
[1] TEAEs are coded based on MedDRA version 18.0. A subject is counted at most once within a preferred term and within an SOC. Table is sorted by SOC in alphabetical order followed by preferred term by decreasing incidence.
[2] Related = possibly or probably related to the study drug, in the judgment of the Investigator.
MedDRA = Medical Dictionary for Regulatory Activities; mos = month; SOC = system organ class; TEAE = treatment-emergent adverse event.

Subjects Age 2 months to < 2 years

A total of 86 TEAEs were recorded in the 2 months to <2 years cohort. At least 1 TEAE was reported for each of the 10 subjects. The SOCs most affected were Gastrointestinal disorders and Infections and infestations (7 [70.0%] subjects each); Metabolism and nutrition disorders (5 [50.0%] subjects); Respiratory, thoracic and mediastinal disorders and Skin and subcutaneous tissue disorders (4 [40.0%] subjects each); and General disorders and administration site conditions and Investigations (3 [30.0%] subjects each). The most frequently reported TEAEs by preferred term were upper respiratory infection and vomiting (4 [40.0%] subjects each); hyperammonaemia, pyrexia, and viral infection (3 [30.0%] subjects each); and constipation, cough, croup infectious, gastroenteritis, hypophagia, metabolic acidosis, nasopharyngitis,

otitis media, urinary tract infection, and rash (2 [20.0%] subjects each). No other TEAE was reported for more than 1 subject.

TEAE Severity

Most of the TEAEs were Grade 1 or Grade 2 (mild or moderate). Grade 1 TEAEs were reported for 3 (30.0%) subjects for a total of 35 events, and Grade 2 TEAEs were reported for 3 (30.0%) subjects for a total of 36 events. There were nine Grade 3 TEAEs reported. The Grade 3 events were hyperammonaemia (2 [20.0%] subjects; 1 event in 1 subject and 4 events in 1 subject, ammonia increased and hypophagia (1 event each in 1 [10.0%] subject [both events in the same subject]), and gastroenteritis and urinary tract infection (1 [10.0%] subject each). There were four Grade 4 TEAEs, which were 2 incidences of cyanosis and 2 incidences of apnoeic attack, all in 1 subject (10.0). Two TEAEs (both in the same subject) had a fatal outcome (i.e., Grade 5), pneumatosis intestinalis and peritonitis, in 1 subject resulting from intestinal perforation after gastrostomy-jejunostomy tube placement leading to peritonitis, pneumatosis, and septic shock.

Discontinuations

1 subject (10.0%) had 3 TEAEs leading to study drug discontinuation. (Pneumatosis intestinalis, peritonitis and hyperammonaemia. All 3 of these events were SAEs, and led to discontinuation of study drug. None of the events were considered related to study drug. The patient subsequently died.

TEAE Relationship to Study Drug

A total of 8 TEAEs that were considered by the Investigator to be related to the study drug were reported in a total of 4 subjects (40.0%). The study drug-related TEAEs, reported for 1 subject (10.0%) each, were constipation, diarrhoea, ammonia increased, carbon dioxide decreased, eczema, nail ridging, and rash (2 events in 1 subject) Ammonia increased, carbon dioxide decreased, nail ridging, and rash (both incidences) were Grade 1; and constipation, diarrhoea, and eczema were Grade 2. None of the study drug-related TEAEs was Grade 3, Grade 4, or Grade 5. None of the related TEAEs was an SAE.

Serious adverse event / deaths / other significant events

Birth to <2 months cohort

In the age birth to < 2 months cohort of the paediatric study HPN-100-009, 11 subjects (68.8%) had at least 1 treatment-emergent SAE.

The SOCs with the most SAEs were Infections and infestations (8 [50.0%] subjects) and Metabolism and nutrition disorders (6 [37.5%] subjects).

There were no SAEs considered related to the study drug. The SAEs occurring in >1 subject were hyperammonaemia (5 [31.3%] subjects) and vomiting (2 [12.5%] subjects).

The percentage of subjects with SAEs was similar in the 2 age groups (age <1 month vs. age 1 month to <2 months). Seven subjects (70.0%) age <1 month and 4 subjects (66.7%) age 1 month to <2 months had at least 1 SAE. All 5 of the SAEs of hyperammonaemia occurred in subjects age <1 month (5/10 [50.0%] subjects); while both of the SAEs of vomiting occurred in subjects age 1 month to <2 months (2/6 [33.3%] subjects).

2 months to <2 years cohort

In the 2 months to <2 years cohort, 6 subjects (60.0%) had at least 1 treatment-emergent SAE. A total of 25 treatment-emergent SAEs were recorded. The most frequent treatment-emergent SAE was hyperammonaemia. A total of 7 SAEs of hyperammonaemia were recorded in 3 subjects (30.0%): 1 subject had 4 events, 1 subject had 2 events, and 1 subject had 1 event. The other treatment-emergent SAEs were the following (by subject): pneumatosis intestinalis and peritonitis (in 1 subject); urinary tract infection (in 1 subject); viral infection, croup infectious, and influenza (in 1 subject); 2 events of apnoeic attack, 2 events

of cyanosis, and gastroenteritis (in 1 subject); and ammonia increased, viral infection, rhinovirus infection, viral upper respiratory infection, asthma, status asthmaticus, and pyrexia (in 1 subject).

Of the 25 treatment-emergent SAEs recorded, most were Grade 2 or Grade 3 (11 events and 8 events, respectively).The Grade 3 (severe) SAEs occurred in 2 (20.0%) subjects and were hyperammonaemia (5 events) and gastroenteritis, urinary tract infection, and ammonia increased (1 event each). The four Grade 4 (life-threating/disabling) SAEs were 2 incidences of cyanosis and 2 apnoeic attacks, all occurring in the same subject. The Grade 5 SAEs (fatal outcome) were pneumatosis intestinalis and peritonitis in 1 subject. The two Grade 5 SAEs and 1 of the cases of Grade 3 hyperammonaemia occurred in the same subject and were the 3 events in the study that led to discontinuation of study drug. None of the treatment-emergent SAEs was considered by the Investigator to be related to the study drug.

Hyperammonaemic crises

A hyperammonaemic crisis was defined as having signs and symptoms consistent with hyperammonaemia (including but not limited to frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high blood ammonia and requiring medical intervention

Birth to <2 months cohort

In the paediatric study HPN-100-009 age birth to <2 months cohort, hyperammonaemic crises were less frequent while subjects were receiving study drug compared to the pre-enrolment period (which for these young subjects was equal to the subjects' age at enrolment). The number of subjects with crises was 7 subjects (43.8%) prior to enrolment, 0 subjects in the transition period, and 5 subjects (31.3%) in the safety extension period. The pre-study rate of crises was 0.017 compared to 0.003 in the safety extension period. All of the hyperammonaemic crises in the safety extension occurred in subjects age <1 month.

2 months to <2 years cohort

In the age 2 month to <2 years cohort compared to pre-enrolment period (subject age in days or 365 days, whichever was less) hyperammonaemic crises became less frequent after subjects began receiving study drug. The percentage of subjects with crises was 6 (60.0%) pre-enrolment, 1 (0.0%) in the transition period, and 3 (33.3%) in the first 6 months of the safety extension period. The median number of crises was 2.0 (range 0-10) prior to enrolment compared to 0.0 in the transition period (range 0-1) and 0.0 in the safety extension period (range 0-4). In the first 6 months of the safety extension period, the majority of subjects (66.7%) had no crises, 2 subjects had 1 or 2 crises (11.1% each), and 1 subject (11.1%) had 4 crises. The pre-study rate of hyperammonaemic crises was 0.011 compared to 0.006 in the safety extension period.

Psychiatric/Nervous System Disorders

Birth to <2 months cohort

In the cohort age 0-2 months, 4 subjects experienced TEAEs of Nervous system disorders or Psychiatric disorders. Of the 4 subjects, 2 (both age 1-2 months) experienced 3 TEAEs of Nervous system disorders, the other 2 (both age < 1 month) experienced 2 TEAEs of Psychiatric disorders. In 3 of the 4 subjects, PAA level was not elevated at time of these events.

One subject in the cohort younger than 2 months old experienced Lethargy and Tremor, both of which were assessed by the investigator as possibly related to RAVICTI. The PAA level in this patient was subsequently reported to be 707 mcg/mL. One day after the Lethargy event resolved, Tremor (a non-serious event) was reported which lasted for approximately 3 months. Plasma ammonia was elevated at 372µmol/L. During the 3 month period, PAA levels and PAA/PAGN ratio remained low and stable.

2 months to <2 years cohort

In the cohort age 2 months – 2 years, only one subject experienced one TEAE of Nervous system disorders, which is apparently a clinical sign of poor growth due to the underlying UCD. Neither ammonia level nor PAA was elevated. No TEAE of Psychiatric disorders was reported.

Laboratory findings

Birth < 2 months

For the majority of the laboratory parameters, the median changes from baseline were generally small, and there were no apparent clinically significant trends over time in the age birth to <2 months cohort or either age group (age <1 month or age 1 month to <2 months.

There were median decreases from baseline at most post-baseline assessments for erythrocytes, haematocrit, haemoglobin, neutrophils, and neutrophil/leukocyte ratio in subjects age <1 month vs. median increases in subjects age 1 month to <2 months. For platelets there was a median increase from baseline at most post-baseline assessments in subjects age <1 month vs. median decreases in subjects age 1 month to <2 months.

2 months to <2 years cohort

Changes from baseline in each laboratory parameter were generally small, and no clinically significant trends in median laboratory parameter values were observed. For each laboratory parameter, the results for the majority of subjects were within the normal range at both baseline and most of safety extension visits.

2.5.1. Discussion on clinical safety

The clinical safety database of paediatric UCD age 0 to <2 months treated with HPN-100 over short and long term safety extension studies includes a total of 16 children < 2months of age and 10 children age 2 months <2years. Five out of the 6 UCD subtypes for which approval is sought are represented in this population. Only 3 subtypes are represented in the 0-<2months cohort. However, as all subtypes have the same clinical sequelae this difference between the two cohorts was not considered important.

The main difference between the two age groups was the incidence of hyperammonaemia which was higher in the under 2-months age group compared to the 2-months to 2-years age group (50.0% vs. 16.7% subjects, respectively. The higher number of reports of hyperammonaemia is not unexpected in the neonatal population who are known to have more severe disease with a high rate of hyperammonaemia. Of the five cases in infants <1 month, 2 were in hyperammonaemic crisis at baseline and a further 3 cases had later onset. Two cases were associated with precipitating factors (URTI, oral candidiasis) 3 cases occurred following dose adjustments. No further warning is recommended on the basis of these findings. However, the wording of section 5.1 has been updated to provide a summary of the 6 cases of hyperammonaemia in the subjects aged up to 2 months of age.

Overall, the data presented indicates that safety profile of glycerol phenylbutyrate is broadly similar between the 0 to <2 months age cohorts and the 2 months <2 yrs age cohorts with some small differences in the frequency of TEAEs reported between age cohorts.

The most frequent study drug-related TEAEs in the 0<2 months age cohort were rash (3 subjects) and diarrhoea (2 subjects). In the 2mth to 2yrs cohort the study-drug related TEAEs were diarrhoea, hyperammonaemia, nail ridging, and rash, each reported for 1 subject each. All were either mild or moderate in severity. None of the related TEAEs was an SAE. Based on these differences, a small number of additional ADRs (constipation and diarrhoea, eczema, nail ridging and rash) were identified in the 2 months – 2 years cohort for inclusion in section 4.8 of the SmPC. The treatment related TEAEs, ammonia

increased, carbon dioxide decreased, identified in the 2 months – 2 years cohort, were considered more likely to be related to the underlying UCD. These events were not included in section 4.8 of the SmPC.

There was one death resulting from intestinal perforation after gastrostomy-jejunostomy tube placement leading to peritonitis, pneumatosis, and septic shock (not related to study drug).

Most of the TEAEs were mild or moderate in severity and considered by the investigator to be unrelated to the study drug. The AE profile in both the 0 to <2 months and 2mths to <2 years cohort was generally consistent with the known safety profile of Ravicti. Of note ADRs were reported in the Blood and Lymphatic disorders SOC for patients in the <2 month age cohort which are not included in the currently approved overall safety profile for Ravicti. Following review of the reported TEAEs, anaemia and thrombocytosis have been added in Section 4.8 of the SmPC for paediatric patients.

PAA toxicity with neurological manifestations has been demonstrated with IV administration of PAA in cancer patients. Higher PAA levels were noted in the 0-<2month age cohort (see also Clinical Pharmacology section of this report). In 3 of the 4 subjects in the 0-2month age cohort who experienced neurological or psychiatric events, PAA level was not elevated at time of these events. One subject experienced neurological events (lethargy , tremor) and also high levels of PAA. However, based on the clinical details of this case, no PAA toxicity or correlation between PAA level and TEAE incidence could be recognised.

Based on the available data, the current warnings on PAA toxicity are considered sufficient to manage this risk in the 0-<2month age cohort.

2.5.2. Conclusions on clinical safety

Ravicti appears to be generally well-tolerated in paediatric patients aged up to 2 months as in the already authorised patients from 2 months to <2 years. Despite some differences in frequencies of AEs, the safety profile for the two age cohorts were broadly similar overall and generally consistent with the known safety profile of Ravicti.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

2.6.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ravicti is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The urea cycle is the metabolic pathway that transforms nitrogen to urea for excretion from the body. Deficiency of an enzyme in the pathway causes a urea cycle disorder (UCD), including deficiencies of carbamoyl phosphate synthetase I (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS, also called citrullinemia type I), argininosuccinate lyase (ASL, also called argininosuccinic aciduria), arginase I (ARG) and ornithine translocase (also called HHH [Hyperammonaemia-Hyperornithinaemia-Homocitrullinuria Syndrome]). All except for arginase deficiency, result in hyperammonaemia and life-threatening metabolic decompensations in infancy. Survivors of the metabolic decompensation frequently have severe neurologic injury. Treatment, as soon as a UCD is suspected, is necessary to remove nitrogen (ammonia) from the body.

3.1.2. Available therapies and unmet medical need

There are limited treatments available for UCD. In addition to Ravicti, there is one alternative pharmacologic therapy for hyperammonaemia licensed for use in the EU sodium phenylbutyrate (NaPBA; Ammonaps and Pheburane).

3.1.3. Main clinical studies

Paediatric study HPN-100-009 was an open-label study consisting of a treatment transition period to Ravicti, followed by a safety extension period for at least 6 months and up to 2 years of treatment with Ravicti. It was designed to capture information important for evaluating safety, efficacy, and PK of Ravicti in young children under 2 years of age with UCDs to support extension of the indication for use for Ravicti to children <2 months of age.

3.2. Favourable effects

Mean blood ammonia levels during long-term open-label HPN-100 treatment were within normal limits for up to 12 months in most paediatric patients 0-<2months and 2months -<2 years throughout the 24-month treatment period.

For subjects age 0 to <2 months ammonia control during dosing with Ravicti in Study HPN-100-009 was broadly comparable (albeit normalised mean ammonia levels were slightly higher) with pooled analysis of long-term ammonia in UCD Patients 2 months to <2 years of Age and age 2-5years in the 12-month extension phase of the HPN-100-012 (HPN-100-012SE) in the original application.

In Study HPN-100-009 all subjects regardless of their status at study entry successfully transitioned to Ravicti, defined as no clinical signs of hyperammonaemia and plasma ammonia <100 µmol/L.

Short and longer-term ammonia control with HPN-100 treatment was achieved among most paediatric UCD patients age 0-<2months and 2months -<2 years.

Plasma concentrations and AUC of PBA were in the same range in subjects with UCDs aged 0 to<2 months as those observed 2months to 2 yrs. which suggest comparable ability to break down Ravicti. However, PAA and PAGN exposure, were generally higher among patients <2 months of age compared with patients age >2 months, as their blood levels are correlated with the patients BSA.

3.3. Uncertainties and limitations about favourable effects

Rigorous evaluation of the clinical benefit of Ravicti in the paediatric population would require a long term active comparator controlled study with clinical endpoints related to hyperammonaemia and its consequences. The demonstration of nitrogen scavenging is an essential but surrogate part of demonstrating the product's benefit in terms of prevention of clinically manifest hyperammonaemia and its complications.

For ethical and logistical reasons such a study is not feasible and instead a long term open label study with two age cohorts (0 -<2months and 2months <2years) was conducted. The demonstration of approximately equivalent pharmacokinetics and efficacy of Ravicti in the two age cohorts is suggestive of similar clinical performance between these two groups.

3.4. Unfavourable effects

The most frequent study drug-related TEAEs in the 0<2 months age cohort were rash (3 subjects) and diarrhoea (2 subjects). In the 2mth to 2yrs cohort the study-drug related TEAEs were diarrhoea, hyperammonaemia, nail ridging, and rash, each reported for 1 subject each.

There were more subjects aged <2 month with TEAEs in the gastrointestinal disorders, metabolism and nutrition, skin and subcutaneous tissue disorder, respiratory, infections and infestations, investigations disorders and blood and lymphatic system disorders SOCs compared to the 2mth to 2yrs cohort.

There were 2 events in the psychiatric disorder SOC, agitation and irritability and 3 events in the nervous systems disorders SOC, 2 events of lethargy and 1 event of tremor. Of these, two neurological TEAE in the 1-<2months age group (tremor and lethargy) were treatment related AEs. There was 1 nervous system SOC event in the 2 months <2yrs (gross motor delay).

The commonest SAE in both populations was hyperammonaemia. All 5 of the SAEs of hyperammonaemia in the 0<2 month cohort occurred in subjects age <1 month (5/10 [50.0%] subjects).

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited, due to the difficulty in conducting studies in the paediatric UCD population.

There were some differences in the frequency of TEAEs reported by patients during HPN-100 treatment in the two age cohorts. This included a small increase in the number of nervous system /psychiatric system adverse events however there was no suggestion of neurotoxicity in the patients experiencing those events.

3.6. Effects Table

Table 4. Effects Table for Ravicti as an as adjunctive therapy for the chronic management of patients less than 2 months of age with urea cycle disorders (UCDs (data cut-off: 17 July 2017)

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
Controlled ammonia levels	No clinical symptoms of	N (%)	8/14 (57.1%) at month 1 3/4 (75%) at	Small numbers, uncontrolled data	HPN-100-009

Effect	Short description		Unit	Treatment	Uncertainties / Strength of evidence	References
		hyperammonaemia and ammonia <100 µmol/L		month 15		
Unfavourable Effects						
Hyperammonaemia			N	5	Small numbers, difficult to ascertain causality	HPN-100-009-safety extension
Psychiatric/ nervous system AEs		Reactions in Psychiatric disorder and Nervous system SOCs	N	5		

Abbreviations: AEs: Adverse events, SOC: System Organ Class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Paediatric patients with hyperammonaemia are at a high risk of death or severe neurological impairment if not treated urgently with a nitrogen scavenger.

Mean blood PAA and urinary PAGN levels in the 0-<2months and 2 months <2years age cohorts provide evidence for the appropriate pancreatic lipase hydrolysis of the glycerol phenylbutyrate molecule with subsequent absorption of PBA and metabolism to PAA demonstrating absorption and conversion of the prodrug Ravicti to its active moiety. The presence of urinary PAGN as the final metabolic end product is evidence of successful scavenging of nitrogen and bypassing of the urea cycle defect. Efficacy and safety outcomes are comparable for the two age cohorts 0<2moths and 2 months <2years. The unfavourable effects of the compound are generally relatively minor. The safety profile of glycerol phenylbutyrate is being further characterised in the ongoing long-term prospective non-interventional registry in patients with UCDs.

3.7.2. Balance of benefits and risks

Evidence of efficacy of glycerol phenylbutyrate in patients 0<2moths has been adequately demonstrated.

As no important new safety signals were identified in patients aged < 2 months compared paediatric patients ≥2 months or adult patients, the current warnings in the product information are expected to be adequate to manage the known risks associated with glycerol phenylbutyrate use.

3.8. Conclusions

The overall B/R of Ravicti is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 - Extension of indication to include in the authorised indication the new paediatric population from 0 to 2 months for RAVICTI based on the final results from study HPN-100-009, an Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate in Pediatric Subjects under Two Years of Age with Urea Cycle Disorders (UCDs); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

This submission covers as well the requirement to submit clinical studies in the paediatric population in accordance with Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') for study HPN-100-009.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0191/2018and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.