24 September 2015
EMA/676925/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ravicti

International non-proprietary name: glycerol phenylbutyrate

Procedure No. EMEA/H/C/003822/0000

Note

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

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List of abbreviations

µg	microgram
µmol	micromole
14C	carbon radiolabel
4-PBA	4-phenylbutyric acid or phenylbutyrate (PBA)
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
ASL	argininosuccinate lyase
AST	aspartate aminotransferase
ASS	argininosuccinate synthetase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration versus time curve
AUC	area under the curve
AUC_{0-24}	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
CEL	carboxyl ester lipase
CFR	Code of Federal Regulations
CHMP	committee for medicinal products for human use
CHO	Chinese hamster ovary
CI	confidence interval
CITRIN	aspartate glutamate transporter deficiency; also referred to as Citrullinemia II
C_{max}	maximum plasma concentration
C_{max-ss}	maximum plasma concentration at steady state
C_{min}	minimum plasma concentration
CNS	central nervous system
CoA	coenzyme A
CPS	carbamoyl phosphate synthetase
CSR	clinical study report
CYP	cytochrome P450
e.g.	for example
ECAC	executive carcinogenicity assessment committee
ECG	electrocardiogram
EMA	European Medicines Agency
EOP2	end of phase 2
EU	European Union
FDA	Food and Drug Administration
Fe	fraction excreted in urine
GCP	good clinical practices
GD	gestation day
GLP	Good Laboratory Practice
GPB	glycerol phenylbutyrate
GPB	glycerol phenylbutyrate (formerly referred to as glyceryl tri-(4-phenylbutyrate)
GT4P	glycerol tri-(4-phenylbutyrate) (now referred to as glycerol phenylbutyrate)
GT4P-F	80% formulation of glyceryl tri-(4-phenylbutyrate)
h	hour
HAC	hyperammonemic crises
HCD	historical control database

HE	hepatic encephalopathy
HEK	human embryonic kidney
hERG	human ether-a-go-go related gene
HHH	hyperornithinemia–hyperammonaemia–homocitrullinuria (HHH syndrome); also referred to as ornithine translocase deficiency
HPN-100	glycerol phenylbutyrate, formerly glyceryl tri-(4-phenylbutyrate)
HPN-100	GPB; assigned the compound code HPN-100 by Hyperion Therapeutics, Inc.
IC50	concentration of inhibition by 50%
ICH	International Conference on Harmonisation
IND	investigational new drug
IQ	intelligence quotient
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
K_i	inhibition constant
LOQ	limit of quantification
LSM	least squares mean
MAA	Market authorization application
mL	milliliter
MTD	maximum tolerated dose
NAGS	*N*-acetylglutamate synthase
NaPAA	sodium phenylacetate
NaPBA	sodium phenylbutyrate
NDA	new drug application
NOAEL	no observed adverse effect level
NOEL	no effect level
ODD	orphan drug designation
OLFS	open-label fixed-sequence
OTC	ornithine transcarbamylase
PAA	phenylacetate/phenylacetic acid
PAA	phenylacetic acid
PAG	phenylacetylglycine
PAGN	phenylacetylglutamine
PBA	(formerly 4-)phenylbutyrate/(formerly 4-)phenylbutyric acid
PBA	phenylbutyrate or 4-phenylbutyrate
PBG	phenylbutyrylglycine
PBGN	phenylbutyrylglutamine
PD	pharmacodynamic
PDCO	paediatric committee
PIP	paediatric investigational plan
PK	pharmacokinetic
PLRP2	pancreatic lipase related protein 2
PND	postnatal day
PopPK	population pharmacokinetics
PR	electrocardiographic interval
PREA	paediatric research development act
PTL	pancreatic triglyceride lipase
QRS	electrocardiographic wave (complex or interval)
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
QTc (interval)	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	scientific advisory panel
SAP	statistical analysis plan
SAP	scientific advisory panel
SD	standard deviation
SE	safety extension
SE	standard error
SIF	simulated intestinal fluid

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
Tmax	time to maximum plasma concentration
UCD	urea cycle disorder
ULN	upper limit of normal
U-PAGN	urinary PAGN
$U\text{-}PAGN_{0\text{-}24}$	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. Submission of the dossier

The applicant Horizon Therapeutics Limited submitted on 2 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for RAVICTI, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2013.

RAVICTI, was designated as an orphan medicinal product EU/3/10/733-739 on 10/06/2010. RAVICTI was designated as an orphan medicinal product in the following indication: treatment of the following UCD sub-types:

• Treatment of carbamoyl –phosphate- synthase 1 deficiency. (CPS)

• Treatment of ornithine carbamoyltransferase deficiency (OTC),

• Treatment of argininosuccinic aciduria(ASS),

• Treatment of hyperargininaemia

• Treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome)

• Treatment of citrullinaemia (CITRIN) type 1 and type II

The applicant applied for the following indication:

“RAVICTI is indicated 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 synthetase I (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS, also called citrullinemia I), argininosuccinate lyase (ASL, also called arginosuccinic aciduria), arginase I (ARG), CITRIN (also called citrullinemia II) and ornithine translocase (also called HHH [Hyperammonaemia-Hyperornithinemia-Homocitrullinemia Syndrome]) 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 patient less than 2 months of age and/or patients with N-acetylglutamate synthase (NAGS) deficiency has not been established.”

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ravicti as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated

that glycerol phenylbutyrate was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 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).

At the time of submission of the application, the PIP P/0068/2014 was not yet completed as some measures were deferred.

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.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance glycerol phenylbutyrate contained in the above medicinal product to be considered as a new active substance in comparison to sodium glycerol phenylbutyrate previously authorised in the Union and claimed that glycerol phenylbutyrate differs significantly in properties with regard to safety and efficacy from the already authorised substances.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 18/11/2010. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Ravicti has been given a Marketing Authorisation in the United States on 1 February 2013.

A new application was filed in Canada.

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: David Lyons

- The application was received by the EMA on 2 June 2014.
- The procedure started on 25 June 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 September 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2014.
- During the meeting on 23 October 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 June 2015.
- During the CHMP meeting on 25 June 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 September 2015 .
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to RAVICTI.

2. Scientific discussion

2.1. Introduction

Urea cycle disorders (UCDs) are very rare, serious and life threatening disorders comprising a group of inherited deficiencies of one of the enzymes or transporters involved in the urea cycle, which converts ammonia to urea. The absence or severe dysfunction of the enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients (Brusilow, 1996). Although genetically distinct, the UCDs share important features and are therefore typically considered as a group. The most important clinical manifestations common to UCDs are attributable to hyperammonaemia. Management of the individual UCD subtypes is generally similar and involves decreasing ammonia production through reduction of protein in the diet, removal of excess ammonia via waste nitrogen scavenging drugs (e.g., NaPBA) and replacement of certain urea cycle intermediates (Table 2 below).

Only a minority of UCD patients are diagnosed based on newborn screening (i.e., argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase (ARG) deficiency subtypes), and most UCD patients are therefore diagnosed after presenting with symptoms of hyperammonaemia. Because even severe (e.g., seizures, cerebral oedema, hyperventilation, posturing, coma) as well as more subtle (e.g., loss of appetite, headache, cyclical vomiting, somnolence, lethargy, fatigue,

disorientation, behavioural abnormalities, sleep disorders, delusions, hallucinations, psychosis, headaches, nausea, vomiting) manifestations are nonspecific, long delays in diagnosis are common (Rüegger, 2014, Nassogne, 2005). Some critically ill infants are misdiagnosed, for example, with sepsis, resulting in delayed treatment or death (Leonard, 2002).

The table below provides further information on the different subtypes of UCD, including their management. For each subtype information whether the orphan designation was requested is also mentioned.

Affected Enzyme or Transporter (other names, inheritance)	**Management[1]**	**Comments[2]**	**Orphan Designation Requested**
Ornithine transcarbamylase (OTC deficiency; X-linked)	Protein restriction, dietary supplements, sodium phenylbutyrate (NaPBA) and sodium benzoate frequently used	Neonatal onset common; female survivors account for most patients	Yes
Argininosuccinate synthetase (ASS deficiency or citrullinemia type I); autosomal recessive	Protein restriction, dietary supplements, NaPBA and sodium benzoate frequently used	Neonatal onset common	Yes
Carbamoyl phosphate synthetase I (CPS deficiency; autosomal recessive)	Protein restriction, dietary supplements, NaPBA and sodium benzoate frequently used	Neonatal onset common	Yes
Argininosuccinate lyase (ASL deficiency, arginosuccinic aciduria; autosomal recessive)	Protein restriction, dietary supplements, NaPBA and sodium benzoate sometimes used	Neonatal or late onset; sometimes associated with liver impairment	Yes
Arginase (ARG deficiency; autosomal recessive),	Protein restriction, dietary supplements, NaPBA sometimes used	Typically insidious or late onset; hyperammonemia less frequent or severe than in other subtypes	Yes
N-acetyl glutamine synthetase (NAGS deficiency; autosomal recessive)	Protein restriction, dietary supplements; Carbglu® ; NaPBA rarely used	Late or neonatal onset[3]	No
Ornithine translocase deficiency (hyperornithinemia, hyperammonemia, homocitrullinuria or HHH Syndrome; autosomal recessive)	Protein restriction, dietary supplements, NaPBA and sodium benzoate sometimes used	Typically late onset	Yes

Affected Enzyme or Transporter (other names, inheritance)	Management[1]	Comments[2]	Orphan Designation Requested
Aspartate glutamate transporter (citrin deficiency or citrullinemia type II; autosomal recessive)	High protein and lipid diet, dietary supplements, NaPBA	Typically late onset although may present in neonatal period with cholestatic hepatitis, citrullinemia and hyperammonemia[4]	Yes

In the EU, the only drug therapy approved for the treatment of UCDs include sodium phenylbutyrate (NaPBA) or carglumic acid for treatment of *N*-acetylglutamate synthase (NAGS) deficiency (approved both in the EU and US as CARBAGLU®). The tablet and powder formulations of sodium phenylbutyrate (NaPBA) were approved in the US in 1996 as BUPHENYL®, in the EU in 1999 as AMMONAPS® and in 2013 as PHEBURANE® (different -formulation of the AMMONAPS powder) as adjunctive therapy in the chronic management of patients with carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS) deficiencies with neonatal onset deficiency and in patients with late-onset disease (presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

Based on data from various sources including the UCD Consortium sponsored and NIH-funded Longitudinal Study is estimated that there are approximately 2000 patients with UCDs in the US, approximately half of whom are diagnosed and approximately 400 of whom are taking NaPBA. The number of undiagnosed patients represents an educated guess based on estimates of incidence and the fact that only about one-third of UCD patients are detected by current newborn screening techniques (Summar, 2013).

Since currently available data suggest that the overall prevalence of UCDs and distribution of subtypes is similar in Japan, North America and Europe (Summar, 2013, Auray-Blais, 2007, Applegarth, 2000), it is estimated that the number of UCD patients in EU member states is about 3400 patients, approximately half of whom are diagnosed and less than 700 patients taking NaPBA).

Elevated blood ammonia; i.e., hyperammonaemia, is the central problem in patients with impaired urea formation. A complete inability to synthesize urea can result in dramatic hyperammonaemia leading to coma and death shortly after birth, whereas less severe defects in urea formation are typically associated with lesser degrees of hyperammonaemia and often present somewhat later in life. UCD management is aimed at prompt diagnosis and reducing production of ammonia through dietary protein restriction and, for patients in whom dietary measures are insufficient, control of blood ammonia through the use of waste nitrogen–scavenging drugs such as HPN-100 and NaPBA.

RAVICTIi (HPN-100) is a prodrug of phenylbutyric acid (PBA) and shares the same mechanism of action and metabolic pathway as NaPBA. It is hydrolyzed to glycerol and PBA in the gastrointestinal tract via pancreatic lipases. Because hydrolysis presumably only begins after HPN-100 exits the stomach and enters the proximal small intestine where it is exposed to pancreatic lipases, PBA delivered orally as HPN-100 enters the circulation about 75% more slowly than when delivered orally as NaPBA. Intact HPN-100 is not detected in the circulation of animals or humans.

PBA is converted via β-oxidation to its active metabolite phenylacetic acid (PAA) (Kormanic, 2012), which is conjugated with glutamine to form phenylacetylglutamine (PAGN), which mediates waste

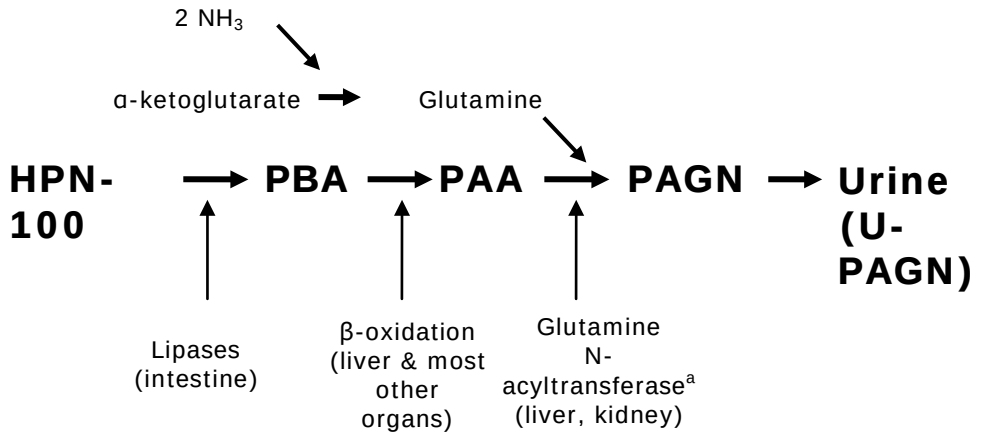
nitrogen removal through urinary excretion. Because glutamine contains two nitrogen atoms, excretion of one mol of PAGN results in removal of two moles of nitrogen, the same as when urea is excreted in urine. Not only does glutamine participate in this alternative pathway for elimination of waste nitrogen, but glutamine levels correlate with plasma ammonia levels and symptoms in UCD patients, and its intracellular accumulation in glial cells is believed to mediate cerebral oedema (Butterworth, 2009; Maestri, 1992; Tuchman, 2008).

The development of HPN-100 builds upon more than 30 years of published clinical experience with the use of sodium phenylacetate (NaPAA) and NaPBA for treatment of UCDs as well as 15 years of post-marketing experience with NaPBA. The rationale for clinical development of HPN-100 was to offer to UCD patients an alternative to NaPBA with sustained-release characteristics that would provide better nitrogen-scavenging and ammonia control, in a formulation that does not contain sodium or sugar, eliminates the substantial pill burden, as well as the bad taste and odour associated with NaPBA, which are reported to compromise compliance in many patients.

2.2. About the product

Glycerol phenylbutyrate (HPN-100) is a nitrogen-binding agent. HPN-100 consists of three molecules of phenylbutyric acid (PBA) joined to glycerol by ester linkage to form a short-chain triglyceride, which appears to be digested by pancreatic lipases to release PBA (Lowe, 2009). Because the synthesis of each molecule of glutamine requires two nitrogen molecules, the body excretes two nitrogen molecules with each molecule of phenylacetylglutamine (PAGN). This is the same stoichiometry as for urea, each molecule of which also contains two nitrogen molecules. The biotransformation of HPN-100 is summarized in the following figure:

Biotransformation of HPN-100 (glycerol phenylbutyrate)



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

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

Overall, plasma concentrations of PBA and its metabolites in adults generally displayed less fluctuation following HPN-100 as compared to NaPBA treatment. In studies involving a comparison of TID dosing with HPN-100 versus NaPBA, the fluctuation between minimum and maximum metabolite levels in

plasma (C_{min-ss} versus Cmax-ss and decreasing again to C_{min-ss}) was less pronounced in adult patients with UCDs after dosing TID with HPN-100 than with NaPBA. These differences in plasma fluctuation are consistent with the conclusion that in adults, PBA delivered as HPN-100 is absorbed more slowly from the gastrointestinal tract than when delivered as NaPBA, presumably reflecting the time required for digestion of HPN-100 by pancreatic lipases. Slower absorption of PBA results in more sustained levels of the active downstream metabolites, PAA and PAGN. The results suggest further that despite differences in plasma metabolite levels with HPN-100 and NaPBA, the extent of PBA absorption as measured by U-PAGN is very similar for the two drugs. This disparity in plasma level and U-PAGN likely reflects the fact that PBA undergoes variable fractional conversion to PAA and PAGN during first-pass metabolism and prior to reaching the systemic circulation.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as an oral liquid containing 1.1 g per ml glycerol phenylbutyrate as active substance.

The product contains no excipients.

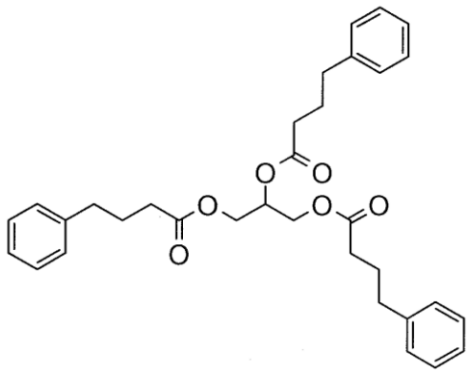
The product is available in clear, type III glass bottles with High Density PolyEthylene (HPDE) child-resistant closure as described in section 6.5. of the SPC. Each carton contains 1 bottle of 25 ml. Each carton contains one bottle and one reclosable bottle cap adaptor.

For the initial prescription, CE marked oral dosage syringes will be provided as a paediatric starter pack.

2.3.2. Active Substance

General information

The chemical name of the active substance is 1,2,3-Propanetriyl tris(4-phenylbutanoate) (INN: glycerol phenylbutyrate) and has the following structure:



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

Glycerol phenylbutyrate is a clear, colourless to pale yellow liquid with a density of 1.1 g /ml which is insoluble in water, but freely soluble in toluene and acetone.

Glycerol phenylbutyrate has a non-chiral molecular structure.

The methods used for elucidation of structure and characterisation were elemental analysis, infrared (IR) spectroscopy, ultraviolet (UV)-visible spectroscopy, mass spectroscopy, nuclear magnetic resonance spectroscopy (1H-NMR and 13C-NMR), optical rotation, thermal analysis and residue on ignition all of which support the chemical structure.

In accordance with Article 8.3 of Directive 2001/83/EC, New Active Substance status was claimed.

Glycerol phenylbutyrate is considered as a derivative of sodium phenylbutyrate.

Significant differences in part are linked to the modified release characteristics to provide better efficacy throughout the day vis-à-vis sodium phenylbutyrate and thereby reducing the number of hyperammonemia crisis, whereas reference is made to the clinical assessment and difference observed in the clinical efficacy/safety of glycerol phenylbutyrate compared to sodium phenylbutyrate.

Manufacture, characterisation and process controls

Originally 2 sources of glycerol phenylbutyrate were proposed. However, one of them has been withdrawn after implementation of an improved manufacturing process by the current manufacturer. Therefore, a number of issues related to the withdrawn manufacturer became obsolete, whereas some data are still used as supportive where applicable.

Glycerol phenylbutyrate is synthesized in multiple steps using well defined starting materials with acceptable specifications.

Information on starting materials is considered acceptable after provision of further information upon request of the CHMP. Sufficient information on raw materials, synthesis and specifications of 4-PBA has been provided and accepted.

No intermediates are isolated in the manufacturing process of glycerol phenylbutyrate. The identified critical steps for the process and their means of control are presented. The process is controlled by a combination of acceptable material specifications and in-process controls (IPCs).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The majority of active substance used in non-clinical and clinical material was then produced by the former manufacturer. In late 2009, an alternative active substance process was developed at the current manufacturer for the proposed commercial manufacturing process with the goal to use a commercially available catalyst and to improve the impurity profile. The synthetic routes are slightly different between the 2 manufacturers. However, characterisation studies revealed the same structure of active substance and comparable impurity profile for the current manufacturer due to the use of different solvents.

All components used in storage of the active substance are safe for pharmaceutical and food use.

Specification

The active substance specification includes tests for appearance, solubility, identification (IR, HPLC), Water Content (Karl Fischer), Assay (HPLC), Related Substance/Impurities (HPLC), Sulphated Ash, Heavy Metals and Residual Solvent (GC). Impurities present at higher than the qualification threshold according to ICH Q3A were qualified and appropriate specifications have been set. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The limit set for unknown/unspecified impurities had initially not been considered acceptable and it has been requested to tighten this limit in line with the ICH Q3A guideline 'impurities in new drug substance'.

An impurity was identified during the stability program and is therefore monitored. Based on *in silico* assessment, no structural alerts were identified for this impurity which has been controlled quantitatively based on additional justification.

Batch analyses data of seven commercial-scale drug substance batches including 3 registration batches, 3 process validation batches and one commercial batch, were provided and demonstrated that the active substance can be manufactured reproducibly.

Stability

Satisfactory stability data according to ICH Q1A on 6 commercial scale batches (3 registration batches, 3 process validation batches) of active substance stored in a representative container closure system for 48 months under long term conditions at 25°C/60% RH and for up to 6 months under accelerated conditions at 40°C/75% RH according to the ICH guidelines were provided. The following parameters were tested: appearance, water content, assay, related substances/impurities (HPLC), microbial limits (total aerobic count, total yeast and mold) and specific pathogens. Glycerol phenylbutyrate (GPB) active substance stability will be continued to be monitored in accordance with the proposed protocol.

Photostability testing was performed according to ICH Q1B. Results showed a very low increase in total impurities when the product is exposed to direct, high intensity light.

The stability results support the proposed retest period of 12 months when stored between 15-30°C.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is intended for oral administration only and is composed of pure glycerol phenylbutyrate (GPB) active substance, a clear colourless to pale yellow liquid. The finished product is undiluted and unformulated GPB drug substance filled into glass bottles.

Glycerol phenylbutyrate active substance is a nearly odourless, tasteless liquid that is insoluble in water.

The primary packaging is a 25 ml clear glass bottle capped with a reclosable bottle cap adaptor. Each carton contains 1 bottle of 25 ml. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

In order to address the requirement of supplying liquid paediatric medicine with a measuring device as outlined in the Guideline on pharmaceutical development of medicines for paediatric use, a starter pack consisting of syringes (1ml, 3ml, or 5 ml) and corresponding to 7 syringes of an appropriate size per prescribed dose in total, is proposed for the first prescription (after initiation of treatment only the bottle and cap adapter are provided and syringes need to be bought from the pharmacy). The starter pack will be used for all age groups including paediatric population.

The container closure system was tested for extractables and leachables as well as deliverable volume. The results revealed no safety concern and were deemed satisfaocry.

Dose accuracy with the proposed delivery devices (as described in Section 4.2. of the SPC) has been properly investigated and found acceptable. However dose recovery through feeding tube was only 70% for a 0.5 ml dose. This issue is reflected in Section 4.2. and 6.5. of the SPC. The root cause of the 70% dose recovery for the 0.5 ml dose should be investigated and nasogastric tubes made of alternate materials such as polyvinylchloride or polyurethane should be explored (see 2.3.6. Recommendations for future quality development).

Manufacture of the product and process controls

The finished product manufacturing process consists of the filling of unformulated, neat glycerol phenylbutyrate (GPB) active substance into bottles. In-process checks include fill weight, cap torque removal, and label verification and are adequate for this type of manufacturing process and pharmaceutical form.

Process validation demonstrates that the packaging process for the 25 ml fill bottle is suitable to meet predetermined criteria for fill volume (volume by weight), torque removal testing, and neck banding. Three batches of drug product ranging in scale from 300 kg to 700 kg were used for validation studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: Appearance (Visual), Identification (FTIR), Identification (HPLC), Water Content (Karl Fischer), Assay (HPLC) and Related Substances/Impurities (HPLC).

In-house HPLC methods are used for assay, identification and related substances and have been validated according to ICH Q2 (R1). All other tests carried out on the finished product are in accordance with the European Pharmacopoeia. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 process validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Originally, the proposed shelf life was suggested as 36 months at not more than 25°C.

Stability data of 3 finished product batches produced by the previous finished product manufacturer (but with the active substance from the current active substance manufacturer) stored under long term

conditions for 24 months at 25°C / 60% RH and for up to 6 months under accelerated conditions at 40°C / 75% RH according to the ICH guidelines were provided.

Stability studies have been carried out on batches of the finished product packaged in the proposed container closure system (upright and inverted).

The following parameters were investigated, using the analytical methods for release of the finished product: appearance, water content, assay, related substances/impurities and microbial limits. The analytical methods were shown to be stability indicating.

Initially, 24 months stability data generated by the previous finished product manufacturer could not be considered as fully supportive as the site has never been registered. A protocol for stability testing with process validation batches manufactured at the approved finished product manufacturer and in accordance with ICH guidelines has been provided. Upon request, further updated stability data (12 months for one batch, 9 months for two batches) from the approved finished product manufacturer have been provided, but the AS had been manufactured by the AS manufacturer no longer used. Scientific discussion on comparative stability data, manufacturing process and container closure system supported the use of the stability data generated by previous finished product manufacturer and eventually a tightened shelf-life of 12 months was considered acceptable. A commitment to provide real time stability data as they become available from the approved manufacturers is also provided.

A photostability study according to ICH Q1B has been undertaken. Clarification with regard to slight increase of impurities in samples exposed to light has been provided and is deemed acceptable.

An in-use stability study was conducted on one batch of finished product. Two bottles of finished product were fitted with reclosable bottle cap adapter, kept in inverted position for 3 days and tested for potency and purity. The results of testing revealed no change in potency and no signs of degradation (impurities) for the duration of the study and support the instruction in the SPC section 6.3 “After the first opening of the medicinal product container, the medicinal product must be used within 3 days”. However the extension of the in-use shelf-life should be investigated to avoid wastage of the finished product when used in paediatric population (see 2.3.6 Recommendations for future quality development).
Based on available stability data, the shelf-life as stated in the SPC (1 year without any special storage conditions) is acceptable.

Adventitious agents

No materials of human or animal origin are used in the active substance or finished product manufacture. A compliance statement certifying the TSE status of the glycerol phenylbutyrate has been provided.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Ravicti is a clear colourless to pale yellow liquid containing 1.1 g glycerol phenylbutyrate per ml. The finished product is intended for oral administration only and is composed of undiluted and unformulated glycerol phenylbutyrate active substance. After implementation of an improved active substance manufacturing process, proof of similarity of active substance has been provided. Satisfactory stability data including comparative stability data support a shelf life that has been

tightened to currently 12 months, whereas real time stability data will be submitted upon availability. A reclosable bottle cap adaptor will be supplied in the outer carton with the medicinal product. For the initial prescription, CE marked oral dosage syringes will be provided as a starter pack (after initiation of treatment syringes need to be bought from the pharmacy).

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1- The root cause of the 70% dose recovery for the 0.5 ml dose should be investigated and nasogastric tubes made of alternate materials such as polyvinylchloride or polyurethane should be explored.

2- The extension of the in-use shelf-life should be investigated to avoid wastage of the finished product when used in paediatric population.

2.4. Non-clinical aspects

2.4.1. Introduction

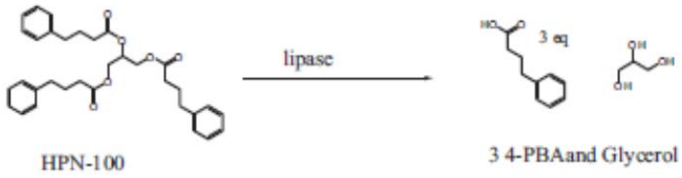
2.4.2. Pharmacology

Primary pharmacodynamic studies

No primary pharmacodynamic studies were performed with GPB or its metabolites (PBA and PAA). This has mainly been described from the scientific literature on PBA, PAA, and PAGN, supplemented in parts with pharmacokinetic and toxicological study observations.

Glycerol phenylbutyrate (GPB) is designed to be a prodrug of PBA, and it consists of three PBA molecules linked via an ester bond to a glycerol backbone. In the gastrointestinal tract digestive lipases facilitate rapid and extensive hydrolysis of GPB, resulting in the production of PBA (Lowe 2009 and **Study A3091-11**). Recombinant human pancreatic lipases, which are present in the gastrointestinal tract of adults and neonates, were shown *in vitro* to hydrolyse GPB to PBA (Figure 2.1.1). The pancreatic lipase related protein 2, carboxyl ester lipase, and pancreatic triglyceride lipase were all shown to cleave PBA from GPB.

Figure 2.1.1: Biochemical Formation of GPB to PBA and Glycerol

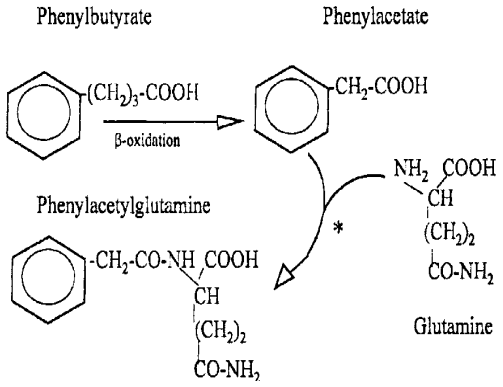


According to Raper (1928), following oral absorption, PBA undergoes β-oxidation to PAA. PAA is the substrate for the metabolic processes that conjugate glutamine in the liver (and kidney) through the enzyme phenylacetyl-coenzyme A (CoA):L-glutamine-N-acetyltransferase to form PAGN (Batshaw, 2001; Moldave, 1957; Webster, 1976), which is subsequently eliminated by glomerular filtration and renal tubular secretion in the urine (James, 1972). An exogenous source of PAA is believed to arise as a breakdown product of phenylalanine by bacteria in the intestine; the endogenous source is from oxidative deamination of phenethylamine (from phenylalanine) and in primates is conjugated with glutamine (Seakins, 1971). PAGN is formed only in higher primates and humans (James, 1972; Kasumov, 2004).

Phenylacetyl-CoA + L-glutamine → CoA + α-N-phenylacetyl-L-glutamine

In animals other than primates, PAA conjugates with glycine (instead of glutamine) to form PAG instead of PAGN (Moldave, 1957). Oral administration of PAA to dogs has there to be increased urinary excretion of glycine 7-fold over 24 h (Quick, 1933). It is noted that this difference in PAA conjugation between primates (including humans) and other mammalian species is related to the substrate specificity of phenylacetyl CoA:acetyltransferase, which is located in the mitochondria of the liver and kidney (Schachter, 1954; Webster, 1976). PAA is also found in urine, conjugated to either glutamine in primates or to glycine in other species, and conjugated to glucuronide (McQuade, 1984; Teuchy, 1971).

Figure 2.1.2: Biochemical Formation of PAGN (Phenylacetylglutamine)



The review is limited, however given the extensive knowledge accumulated for PAA and PBA this is sufficient to demonstrate the pharmacological effect of PBA (pro-drug) and PAA (active moiety) to bind waste nitrogen, and that this is then excreted into the urine as PAGN.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed with GPB or its metabolites. Given the pharmacological nature of GPB and its metabolites this is acceptable.

Safety pharmacology programme

A range of GLP safety pharmacology studies has been performed with GPB using both *in vitro* and *in vivo* models. The organ systems evaluated include the CNS, cardiovascular system and respiratory system (Table 2.3.1).

Cardiovascular system:

An in vitro hERG study was completed using concentrations of PBA (pro-drug) and PAA (active constituent) well in excess of peak plasma exposures observed in clinical studies. Concentrations shown to inhibit peak currents in the hERG assay were 46-fold (PBA) and 24-fold (PAA) in excess to clinically observed levels. The potential of PBA and PAA to affect potassium channel current was reviewed using rabbit cardiac myocytes. It was observed that concentrations of up to 1591.8 µg/mL of PBA and 305.2 µg/mL of PAA caused no change in cardiac myocyte tail currents.

Two in vivo studies have been completed. In the first in telemetered monkeys dosed orally with up to 4 g/kg GPB. No significant treatment-related changes in heart rate or blood pressure were seen at any dose. Treatment with 4 g/kg (48 g/m^2) GPB affected cardiac ion channels (PR, QRS and QTc), and as confirmed below was also associated with CNS depressive effects such as hypo-activity, hunched posture, unsteady gait, piloerection, emesis, and loose faeces. It is possible that these CNS effects may have influenced the cardiac changes, and so a second study to assess the arrhythmogenic potential of GPB was conducted in a Carlsson rabbit model. Rabbits were treated with up to 300 mg/kg GPB and there was no apparent change in cardiac parameters (heart rate, PR interval and QRS duration) detected. A significant increase in arterial blood pressure was observed at both doses tested in this study; the investigators and applicant suggest that this may be confounded by anaesthetic effects (methoxamine and/or the ketamine/xylazine). Blood pressure changes have not been observed in associated studies and this explanation is considered acceptable in view of the limited cardiovascular changes observed.

Central Nervous System:

Adult cynomolgus monkeys were dosed orally with 1 and 4 g/kg GPB. No changes in behaviour or body temperature were detected at 1 g/kg, however at the higher dose there distinct signs of CNS depression occurring up to 24 hours after dosing, including a significant reduction in body temperature. The likelihood for CNS effects following GPB treatment is limited given the high margin of safety.

Respiratory system:

The effect on the respiratory system was investigated using conscious adult cynomolgus monkeys. Oral gavage dosing with GPB had little effect on any respiratory parameter at the high 4 g/kg dose. Overall, there are no issues regarding safety pharmacology identified.

Pharmacodynamic drug interactions

No studies have been conducted to review pharmacodynamic interactions due to the mechanism of action GPB and its downstream products, PBA and PAA. This is considered acceptable based on the pharmacological nature of the product.

2.4.3. Pharmacokinetics

The pharmacokinetics of GPB was investigated after oral administration in the rat and cynomolgus monkey and in vitro by using animal and human tissues.

Absorption

In rats, oral administration at up to 650 mg/kg in male rats and 900 mg/kg in female rats resulted in similar exposure between single and repeat doses. PBA exposure appeared to be lower in males as was total radioactivity, PBA, and PAA compared to females. PAG levels were clearly higher in females after repeated dosing. Radioactivity was rapidly absorbed from the gastrointestinal tract, distributed widely throughout body organs and tissues.

In the cynomolgus monkey, oral administration of a single GPB dose (600 mg PBA equivalents/kg) resulted in systemic exposure to about 10% PBA and to around 40% and 20% of its known metabolites PAA and PAGN, respectively.

Distribution

Oral administration of radiolabeled GPB in the cynomolgus monkey resulted in wide distribution of GPB-related material throughout the body (although the large intestine wall at 8 h post-dose was the only tissue to contain greater than 1% of the administered dose). Tissue concentrations were generally highest at 8 h post-dose and were highest in the large intestine wall, bile, plasma, kidney, liver, urinary bladder, and whole blood. Concentrations generally declined throughout the 72-h period, indicating no accumulation of radioactivity, but radioactivity was still measurable in all but the eyes, cerebrospinal fluid (CSF), and brain at sacrifice.

Overall, concentrations in the tissues of the central nervous system (CNS) were generally one of the lowest measured, indicating that GPB and/or its metabolites did not readily penetrate the blood–brain barrier. Whole blood and blood cell /plasma ratios were <1 at all times, indicating that association of drug-derived material with red blood cells was limited.

In a few tissues, particularly the major excretory organs (i.e., kidney and liver) and the more lipophilic tissues (i.e., skin, fat [peri-renal], and lymph nodes [mesenteric]), the tissue/plasma ratio increased from less than one at 8 h post-dose to 7.9–87 at over 72 h, indicating that drug-derived material was eliminated more quickly from the systemic circulation than from these tissues.

Plasma protein binding

In in vitro studies, plasma protein binding of PBA was moderate to high (up to 87.9–98%) for all species evaluated (mouse, rat, rabbit, monkey, and human). For mouse, rat, monkey, and human plasma, plasma protein binding decreased with increasing dose so that the free fraction increased with PBA concentration. For PAA, plasma protein binding was low to moderate (up to 15.2–76.4%) for all species. Increasing free fractions were noted with increasing concentrations for all species, but only at higher concentrations in mouse and rat plasma. For PAGN, the extent of plasma protein binding was low (1.3–12%) in rats, monkeys, and humans and exhibited no concentration effects.

Metabolism

A series of in vitro studies was conducted to determine the primary enzyme involved in the hydrolysis of GPB and to evaluate the relative risk of metabolism-based drug–drug interaction. The results of these experiments showed that digestive lipases are the main enzymes responsible for hydrolysis of GPB.

The metabolism of GPB was evaluated in vitro using hepatocytes from mice, rats, rabbits, dogs, monkeys, and humans. The results of in vitro and in vivo studies show that in terms of metabolism of PBA and GPB, non-human primates are more closely aligned with human metabolism than are the mouse, rat, and rabbit. As a result the toxicology program has been completed with cynomolgus monkeys (as non-rodent species). This is adequate justification for use of chosen toxicological species.

An in vitro evaluation of the pancreatic lipase activity against GPB showed that pancreatic lipase related protein 2 (PLRP2), carboxyl ester lipase (CEL), and pancreatic triglyceride lipase (PTL) can cleave PBA from GPB. These data suggest that PLRP2 and CEL enzymes play a role in GPB hydrolysis in vivo and may contribute to effective digestion of GPB in the early neonatal period before PTL is present.

Elimination

In rats, PBA/PAA was almost exclusively excreted in urine, with 90-98% total urinary radioactivity recovered by 24 hours post-dose. Approximately 60-90% of the administered dose was excreted in urine as PAG and 3 to 16% as hydroxylated PBA following single and repeat oral doses.

Minor elimination of GPB occurred via faeces, which contained the metabolites PAA and PBA, and in bile, with the major components PAG and PAA. The levels of PAG were higher than PAA following repeat administration in males at the low and high dose, which is consistent with PAA levels increasing over time and indicated a capacity limited step in the metabolism of PAA to PAG. Intact GPB was not detected within the systemic circulation or in any tissues or excreta analysed.

After oral GPB administration, approximately 45% of the dose was eliminated in urine, of which about 87% was in the form of PAGN. A large fraction of the remaining dose (about 25%) was excreted in faeces, of which approximately 85% was in the form of PBA and likely represented unabsorbed GPB that had been hydrolysed after passing through the gastrointestinal tract.

Pharmacokinetic drug interactions

In vitro studies were conducted to evaluate the potential for GPB and PBA to induce and inhibit the cytochrome P450 (CYP) enzymes. In human liver microsomes, both PBA and PAA were reversible inhibitors of human CYP. GPB did not inhibit CYP1A2, CYP2C8, CYP2C19, CYP2D6, or CYP3A4/5. GPB treatment resulted in only slight (19–35%) inhibition of CYP2C9. An in vivo study to examine CYP2C9 inhibition has been initiated by the applicant. The applicant is requested to submit the results by October 2015.

The effects of PBA and PAA on CYP activity were greater than that seen with GPB. With PBA, more than 60% inhibition occurred with CYP2C9, CYP2D6, and CYP3A4/5 (testosterone 6β-hydroxylase activity only). PAA treatment resulted in ≥ 37% inhibition for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Generally, inhibition at the 0 time point was similar to or less than at the 30-min incubation time point, indicating that there was no time-dependent inhibition with GPB, PBA, or PAA and that inhibition was reversible.

In cultured human hepatocytes, both PBA and PAA exhibited minimal induction of CYP1A2 and CYP3A4/5.

It is noted that in human plasma and microsomes the half-lives for GPB hydrolysis were longer than that seen with lipase, so suggests that GPB is most likely hydrolysed in the gut lumen by digestive lipase, and therefore preventing direct intestinal absorption of GPB. As a result the applicant suggests that there may be limited risk of esterase or CYP450 drug–drug interactions attributable to GPB. This seems plausible.

An investigation of PAA as an inhibitor of the drug transporters Pgp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and OCT1 has been initiated. In addition the inhibition of Pgp and BCRP by GPB (HPN-100) will be examined.

Other pharmacokinetic studies

An in vitro study was completed to examine the hydrolysis of GPB and two impurities - tetra-ester 1 and tetra-ester 2. Each was rapidly hydrolysed to PBA in the presence of pancreatin or pancrelipase, indicating that GPB and tetra-esters are rapidly converted to PBA in the gut lumen before they can permeate the intestinal membrane.

2.4.4. Toxicology

Single and repeated oral dose studies were conducted using GPB, in accordance with GLP in mice, rats, and monkeys. A full battery of genotoxicity, carcinogenicity, reproductive and developmental, and juvenile toxicity studies was also conducted using GPB. In addition, the genotoxic potential of the GPB metabolites PBA, PAA, PAGN, and PAG were assessed.

Single dose toxicity

Single dose toxicity studies have been conducted in rats and monkeys. Tolerance to GPB was less so for rats, the maximum tolerated dose (MTD) to rats was 0.9 g/kg/day (5.4 g/m^2), and compared to monkeys which was > 6.5 g/kg (> 78 g/m^2). The applicant has related this potentially due to differences in glycine stores and relative systemic levels of PBA and PAA.

Repeat dose toxicity

The applicant has completed mid to long term repeat dose toxicity studies in three species: mice, rats and monkeys. Mouse studies were designed primarily to establish condition suitable for the 6 month carcinogenicity study in transgenic (Tg.rasH2) mice. Studies in rats were completed with dosing of up to 26 weeks, and in cynomolgus monkeys the duration was extended to 52 weeks.

The data in mice has been utilised in the main to optimise dosing in the 26 week carcinogenicity study in transgenic (Tg.rasH2) mice. Rats were treated with GPB for up to 26 weeks and monkeys for up to 52 weeks.

The applicant has performed a detailed level of studies to investigate potential toxicological consequences of repeated treatment with GPB, and thus extended exposure to its metabolites and active constituent, PBA and PAA, respectively.

The NOAEL in the rat was 0.65 g/kg (3.9 g/m^2); in the monkey, it was 4.5 g/kg (54 g/m^2).

The predominant changes noted in the general toxicology studies following GPB treatment relate to three aspects – changes to the CNS, the liver and the haematopoietic system. It is noted that these studies have been conducted in healthy animals, and differences in the metabolic processes (rats), and retention of nitrogen (monkey) from UCD patients may help explain some of the adverse changes observed in these studies.

Central Nervous System:

Changes to the CNS were first observed in the safety pharmacology studies, in which neuro-behavioural function was affected following acute treatment in monkey studies. This was further observed in mice, rats and monkeys toxicity studies. The CNS effects noted in these studies included tremors, hypoactivity, muscle rigidity, impaired equilibrium and impaired muscle coordination. These

effects were seen across species however they do not appear to be exacerbated on extended treatment with GPB. NOAELs have been established for each species, each being in excess of anticipated clinical exposure. The safety margins from the pivotal chronic studies in rats and monkeys are 5.8 and 4.9 respectively.

Liver:

All species treated with GPB exhibited increased liver weights and this was associated with minimal to mild centrilobular hepatocellular hypertrophy (mice and monkeys). Due to the metabolic process of converting GPB to the PAA, the applicant has detailed that the changes to the liver are the result of adaptive changes occurring in generating PAA, and are the result of hepatic enzyme induction. These changes are seen across species and are further confounded by the use of GPB in animals with a normal functioning urea cycle. It is also considered that the established NOAELs in each species provide a sufficient margin for safety, so these adaptive changes may be of limited concern.

Haematopoietic system:

Changes to the haematopoietic system were generally seen to be mild and not associated with histological correlates as no distinct changes were seen in the bone marrow. In rats and monkeys, the general trend was for reduced RBCs, haemoglobin, haematocrit and platelets. Thymus weights were reduced in rats treated with GPB over 14 days, however this was not seen in the longer duration studies and had no histological correlate so is of limited significance. In addition in monkeys treated for 13-week dosing, 1 male and female each at 1.75 g/kg exhibited a small thymus that correlated with minimal lymphoid depletion. Some females in this study also exhibited enlarged and discoloured lymph nodes at 1.75 g/kg/day. It is agreed that haematopoietic changes can be considered to be mild and sufficient margins for safety are demonstrated.

Genotoxicity

GPB was shown to be non-mutagenic in both in vitro and in vivo studies. Additional in vitro studies were conducted to examine the potential mutagenicity of its metabolites, in which it was shown that PBA, PAA, PAGN, and PAG were negative in Ames, and PAA, PAGN, and PAG were not mutagenic in chromosomal aberration assay. Although PBA was shown to be positive for the induction of structural chromosome aberrations following metabolic activation, these findings were seen at potentially cytotoxic concentration levels, and further clastogenic examination using human peripheral blood lymphocytes was negative. The weight of evidence would suggest negative potential clastogenicity with PBA.

Carcinogenicity

The long term safety of administering GPB was evaluated as part of a standard assay to examine potential carcinogenicity. Two carcinogenicity studies were conducted. The first is a 26 week oral carcinogenicity study in male and female hemizygous Tg.rasH2 mice. Animals were treated daily with oral doses of GPB up to 1 g/kg/day for 26 weeks. No evidence of tumour formation was detected in this study.

In the second study, rats were dosed daily with 0.07, 0.21 and 0.65 g/kg/day to males and 0.10, 0.30 and 0.90 g/kg/day to females of oral GPB for 104 weeks. A number of neoplasms were detected in this study that can be attributed to treatment. It is noted that GPB (PBA/PAA) has already been determined to be non-genotoxic. These include findings of tumours in the adrenal gland, pancreas, thyroid, uterus, Zymbal's gland, and cervix.

In male rats, there were significant increases in incidence of pancreatic acinar cell adenomas (0.21 g/kg/day), pancreatic acinar cell carcinomas (0.65 g/kg/day), adrenal cortical carcinomas (0.21 g/kg/day), thyroid follicular cell adenomas (0.65 g/kg/day) and Zymbal's gland carcinomas (≥0.21 g/kg/day). Pre-neoplastic findings in male rats were also observed as pancreatic acinar cell hyperplasia (0.65 g/kg/day), focal hypertrophy of the zona fasciculata in the adrenal cortex (0.65 g/kg/day) and thyroid follicular cell hyperplasia (≥0.07 g/kg/day).

In female rats, neoplastic changes were noted in the following tissues: pancreatic acinar cell adenomas (0.30 g/kg/day), pancreatic acinar cell carcinomas (0.90 g/kg/day), adrenal cortical carcinomas (0.90 g/kg/day), thyroid follicular cell adenomas and carcinomas (0.90 g/kg/day), Zymbal's gland carcinomas (0.90 g/kg/day), benign endometrial stromal polyps in the uterus (0.90 g/kg/day) and malignant schwannomas in the cervix (0.30 g/kg/day). Pre-neoplastic findings in female rats were also observed as pancreatic acinar cell hyperplasia (0.90 g/kg/day), focal hypertrophy of the zona fasciculata in the adrenal cortex ((≥0.30 g/kg/day), thyroid follicular cell hyperplasia (≥0.10 g/kg/day), cystic endometrial hyperplasia in the uterus (0.90 g/kg/day), increased hepatocellular basophilic foci (≥0.30 g/kg/day) and retinal atrophy in the eyes (0.90 g/kg/day).

The applicant provided a detailed discussion of the neoplastic and pre-neoplastic findings observed in the rats. In addition a Scientific Advisory Panel (SAP) was convened as organised by the MAH, in order to classify the risk associated with each tumour type for the study. The following was concluded for each tumour type:

Adrenal Cortical Lesions: The no tumour effect dose level was considered to be 0.070 g/kg/day in males and 0.3 g/kg/day in females. The proliferative lesions of the adrenal cortex were nonspecific and can be one of the most common findings in endocrine tissues of aged rats. It was acknowledged that previous rodent endocrine tumours seen with non-genotoxic compounds have not been relevant for humans.

Pancreatic Lesions: The no tumour effect dose level was considered to be 0.070 g/kg/day in males and 0.3 g/kg/day in females. Pancreatic acinar cell proliferation appears to be unique in the rat (Dominick et al., 1990; Klaunig et al., 2003). It is noted that acinar cell hyperplasia and adenoma are not precursors of acinar cell carcinomas in humans. The panel highlight the presence of glycerol and butyrate may influence release of cholecystokinin (CCK), which is only mitogenic to rat pancreatic acinar cells, leading to their stimulation and progression from hyperplasia to carcinoma.

Thyroid Lesions:

The no tumour effect dose level was considered to be 0.21 g/kg/day in males and 0.3 g/kg/day in females. It is noted that thyroid tumours lack relevance in humans (Alison et al., 1994; Cohen, 2004) - literature suggest that neoplasia of the thyroid gland has only been observed in humans following exposure to radiation, and not with any chemical. This suggests no relevancy of this finding for human use.

Uterine Lesions:

Cystic endometrial hyperplasia and endometrial stromal polyps were observed with increased incidence in all GPB treated female groups. These findings are commonly seen in aging female rats. Uterine endometrial lesions in humans are mediated by estrogen stimulation and there is no evidence of stimulation of estrogenic activity with GPB in any species in the animal toxicology studies. The presence of endometrial stromal polyps are also common in aging rats, formed possibly due to changes in uterine stromal remodeling that tends to occur in aging rats (Suckow et al. 2006). In addition, there

appears to be no direct histomorphic counterpart in humans to the rat endometrial stromal polyp. It is agreed that there is a case that a carcinogenic risk for humans would be limited.

Zymbal's Gland: Tumours of Zymbal's gland are uncommon in rodents, and additionally there is no corresponding organ in humans so the risk for humans may not be relevant.

Cervical Schwannoma: A non-dose-related increase in malignant schwannomas was observed in the cervix of mid-dose (0.3 g/kg) female rats. The report reviewed by the SAP suggests that the morphology of the rodent neoplasms is not the same lesion as human schwannomas. In these cases, such as in the reproductive tract, they may appear more like primitive mesenchymal tumours than the well-organised structures present in human (Wippold et al., 2007). It is highlighted that there is no dose-response relationship seen in the rat carcinogenicity study, the incidence of cervical schwannomas is highest at 0.3 g/kg/day.

Reproduction Toxicity

Developmental toxicity has been examined in pregnant rats and rabbits in appropriately conducted GLP studies.

A single study was conducted in male and female rats to determine any potential effect GPB (HPN-100) had on reproductive performance and fertility. Animals were treated with GPB with dosing of up to 1.2 g/kg/day. In male rats, there appeared to be no effect of GPB on fertility, on the appearance of male reproductive organs, and on sperm motility and counts. In females all oestrous cycling and mating and fertility parameters were unaffected by dosages of GPB as high as 1.2 g/kg/day.

General toxicity signs were seen in both sexes, predominantly in increased liver weights, decreased weight gain and decreased motor activity. The NOAEL in both male and female rats for general toxicity signs was established as the low dose, 0.65 mg/kg/day, for reproductive performance this was at the mid dose of 0.9 mg/kg/day. These values are supported and allow for sufficient safety margins to the anticipated clinical dose. In rats the applicant has conducted a definitive study in which pregnant rats were orally treated with up to 0.9 g/kg/day GPB once daily gestation days 7–17. Maternal toxic levels were seen at the mid and high doses (0.65 and 0.9 g/kg/day) in which maternal weight gains were reduced. This resulted in reduced fetal weights in these treatment groups (up to 10% loss in fetal weight compared to controls). Fetuses in these dose groups also demonstrated increased incidences of skeletal variations and incomplete ossifications. Based on these results, the developmental and maternal NOAELs of 0.3 g/kg/day (1.8 g/m^2/day) are supported.

In rabbits, in the definitive study pregnant rabbits were treated with up to 0.35 g/kg/day GPB once daily on gestation day 7 through day 19. No developmental effects were observed at any dose in this study, there was no evidence of maternal adverse effects, nor were there any signs to indicate developmental toxicity. There were no changes in fetal weight and no evidence of fetal gross external, visceral, or skeletal malformations or variations. The maternal and developmental NOAEL is agreed as 0.35 g/kg/day (4.2 g/m^2/day). In the earlier conducted dose range finding study in rabbits, adverse changes were observed at doses of 0.6 g/kg/day and mortality was observed at 0.4 g/kg/day, so there is some support that the dose of 0.35 g/kg/day may be a valid estimation for a NOAEL.

There were limited adverse changes observed in the perinatal/postnatal toxicity study conducted in rats. Pregnant rats were administered GPB at 0.3, 0.6, or 0.9 g/kg/day once daily by gavage to pregnant females from GD 7 through lactation day 20. Similar adverse effect seen in the developmental toxicity study was observed at doses of 0.6 and 0.9 g/kg/day, although no changes were observed on pregnancy outcomes. Effects on the F1 generation, i.e. sexual maturation, learning,

memory, and reproductive capacity were absent on all doses tested. The maternal NOAEL for GPB was 0.3 g/kg/day (1.8 g/m^2/day) and the NOAEL for growth and viability of the F1 pups was 0.9 g/kg/day (5.4 g/m^2/day).

In summary, maternal toxicity and adverse effects on embryofoetal development (foetal weights and cervical ribs) were observed in the rat study.

Overall, the risk for developmental toxicity as the result of treatment with GPB at clinical doses is considered to be limited, it is agreed that restrictions to not use RAVICTI during pregnancy and for use of contraception in women of childbearing potential is appropriate.

Juvenile toxicity:

Two studies were completed to examine the effects of GPB on neonatal/ juvenile animals.

In the 13 week repeat dose study in juvenile cynomolgus monkeys previously discussed , the toxicity profile in juvenile animals did not significantly differ from that establish with adult monkey studies with GPB.

The neonatal rat studies were in two parts: the first part of the study conducted from postnatal Day 2-50 examined clinical signs of toxicity to the animals. Rats were treated with up to 1.2 g/kg/day GPB, and the main findings were related to changes to liver markers (ALT and AST were increased in females), reduction in leucocyte counts, and lowered adrenal and ovarian weights. Most of the adverse findings were observed in the high dose group animals, and so a NOAEL for general toxicity in neonatal rats is 0.9 g/kg/day (5.4 g/m^2/day). All treated animals however demonstrated microscopic findings of minimal to mild periductular mixed cellular infiltrates in the liver. These findings were seen in earlier studies with GPB and may be considered to be an adaptive response.

In the second part of this study, pre/post natal development was further examined in the F1 generation of these neonatal rats. Following treatment with GPB some changes were noted in the mid and high dose groups such as reductions in litter size and live foetuses in addition to gross external alterations (umbilical hernia and tail anomalies). A NOAEL for developmental toxicity could not be determined as adverse fetal findings (loss of foetal weight) was observed in all treated groups, so a dose below 0.65 g/kg/day, similar to that seen in the earlier pre/post natal study in rats is most likely.

In summary, the neonatal studies are sufficient to support the proposed paediatric dosing with GPB, toxicity profiles are not adversely different between neonatal and adult rats.

Other toxicity studies

No concerns were raised for local tolerance or immunotoxicity following review of the repeat dose toxicity studies.

Impurities in the drug substance have been adequately qualified in toxicological studies, batch details have been provided in the dossier to support the argument for qualification.

2.4.5. Ecotoxicity / environmental risk assessment

An appended ERA report has been provided, detailing some of the pharmacokinetics of the active substance, glycerol phenylbutyrate, i.e. its active degradation in vivo to PAA and PBA, and the assessment of these components in the ERA as a result.

The result of Phase I assessment reveals that PAA and PBA cannot be considered to be PBT's, although the estimation for PEC surfacewater (3.345 µg/L) is above the action limit to trigger further

investigation in a Phase II environmental fate and effects assessment. Further justification to support the endogenous formation of PAA in animals and humans was provided and the discussion was acceptable, further examination of glycerol phenylbutyrate (PAA/PBA) in a Phase II assessment was deemed unnecessary. The use of glycerol phenylbutyrate, and generation of its metabolites, PBA and PAA, will not pose a risk to the environment. It is agreed that the use of glycerol phenylbutyrate, and generation of its metabolites, PBA and PAA will not pose a risk to the environment.

Summary of main study results

Substance (INN/Invented Name): Glycerol phenylbutyrate – (Metabolites - PBA and PAA)			
CAS-number (if available): 611168-24-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Published literature For PBA and PAA	PBA: 2.42 PAA: 1.41	Potential PBT (N)
PBT-assessment			
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	3.345 with a refined Fpen of 0.0003	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
None provided or necessary (see text)			
Phase IIa Effect studies			
None provided or necessary (see text)			

2.4.6. Discussion on non-clinical aspects

The applicant has performed an adequate non-clinical development programme for GPB, which consisted of a range of safety pharmacology, pharmacokinetic (PK) and toxicology studies. Pharmacodynamic studies have not been conducted by the Applicant but literature and extensive clinical experience is available for PBA which is licensed in the EU in the form of sodium phenylbutyrate (NaPBA) for the treatment of urea cycle disorders.

Toxicity studies were conducted in mice, rats and monkeys, including a full battery of genotoxicity, carcinogenicity and reproductive toxicity studies. The genotoxicity of the GPB metabolites PBA, PAA, PAGN, and phenylacetylglycine (PAG) was assessed in in vitro genotoxicity studies.

The main toxicities observed during the non-clinical development were related to reduced body weight or body weight gain along with microscopic changes in the liver and spleen. The latter toxicities were considered adaptive and secondary to metabolic alterations. Overall, the reviews of the general toxicity studies do not reveal any additional concerns in relation for safety for human administration.

In the rat carcinogenicity study, a number of neoplasms were detected that can be attributed to treatment. These include findings of tumours in the adrenal gland, pancreas, thyroid, uterus, Zymbal's gland, and cervix. The applicant has provided a detailed discussion of the neoplastic and pre-neoplastic findings observed in the rats. In addition a Scientific Advisory Panel (SAP) was convened in order to classify the risk associated with each tumour type.

The applicant has addressed the concern raised for relevance of the tumour findings with greater emphasis attached to the use of historical control incidences and additional literature provided. More in-depth discussions have been provided to explain the relevance of tumours observed in the adrenal gland, the pancreas, thyroid, uterus, Zymbal's gland, and cervix. Potential rat–specific mechanisms for tumour formation were also explored. Overall, it is agreed that the relevance of lesions in the adrenal gland, pancreas, thyroid, uterus and Zymbal's gland to humans would be limited. It is also acknowledged that NaPBA (AMMONAPS), the precursor to the active PAA moiety has been on the market in the EU since 1996 without any significant finding for neoplastic lesions. There is also some limited literature evidence presented to suggest that exposure to PBA may demonstrate some modest improvement in different types of cancer. Further discussion is provided concerning the increased incidence of schwannomas observed in the completed rat carcinogenicity study (Study WIL-671007). A non-dose-related increase in malignant schwannomas was observed in the cervix of mid-dose (8/65 animals, 300 mg/kg) female rats, compared to incidences in the two female control groups (2/65 and 0/65). It is also highlighted that in humans, malignant schwannomas are thought to occur in patients with neurofibromatosis at an incidence of 2-13%.

In summary, most of the Scientific Advisory Panel discussions are supported, including the limited human relevance for malignant cervical schwannomas. The non-clinical data have also been adequately reflected in the SmPC.

Overall no concerns for genotoxicity were raised with GPB and its main metabolites in the completed in vitro and in vivo studies. Further examination of the completed long term studies in rats and the 6 month transgenic mouse study reveals a lack of carcinogenic potential, and it is further confirmed that these rodent studies would have included adequate exposure to all relevant human metabolites. Given the added discussion from the non-clinical studies and lack of malignancy signal observed following clinical exposure to NaPBA, this can be considered sufficiently addressed in the non-clinical part of the application.

Toxicokinetic evaluations were included in all of the repeat dose toxicology studies, in each of the embryo-foetal toxicity study in rats and rabbits and also in the 2 year carcinogenicity study in rats. Exposure to GPB (PBA/PAA/PAG/PAGN) was confirmed in all dosed animals and exposure generally increased on increased dose. There was limited gender variation in exposure and no evidence of accumulation. Overall the Applicant has provided an adequate toxicokinetic programme.

In reprotoxicity studies, maternal toxicity was observed as all as reduced weight in foetuses and cervical ribs. This is adequately described in the SmPC.

Overall, the risk for developmental toxicity as the result of treatment with GPB at clinical doses is considered to be limited, it is agreed that restrictions to not use RAVICTI during pregnancy and for use of contraception in women of childbearing potential is appropriate.

Assessment of paediatric data on non-clinical aspects

In addition, to support the use in paediatric patients the effects of GPB were assessed in juvenile toxicity studies in neonatal rats and juvenile monkeys. This is adequately addressed.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the CHMP considered that the data have been adequately addressed and there are no non- clinical objections to the grant of a marketing authorisation.

2.5. Clinical aspects

2.5.1. Introduction

The rationale for clinical development of HPN-100 was to offer to UCD patients an alternative to NaPBA with sustained-release characteristics that would provide better nitrogen-scavenging and ammonia control, in a formulation that does not contain sodium or sugar, eliminates the substantial pill burden, as well as the bad taste and odour associated with NaPBA, which are reported to compromise compliance in many patients.

The Clinical Development Program includes 10 controlled and uncontrolled clinical studies as summarized in Table 1 below. These studies were performed across three populations (UCD patients, hepatic impaired patients and healthy volunteers); collectively these studies comprise 359 patients/subjects who have received at least one dose of Ravicti. The portion that comprises the target UCD population includes 114 patients with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH syndrome across five short- and long-term clinical studies (UP 1204-003, HPN-100-005, HPN-100-006, HPN-100-007, HPN-100-012), as well as a continued access protocol (HPN-100-011), which is ongoing for six patients in Canada. The portion that comprises the hepatic impaired patient population includes 129 patients from two studies (UP 1204-002, HPN-100-008) and the portion that comprises healthy volunteers includes 116 adults from two Phase 1 single- and multiple-dose pharmacokinetic (PK)/pharmacodynamic (PD) studies (UP 1204-001, UP 1204-002) and a thorough QT/QTc study (HPN-100-010).

The four short-term UCD studies compared 24-hour ammonia control during equivalent steady state dosing with HPN-100 and the approved comparator, NaPBA, in UCD patients ranging in age from two months to over 70 years. In addition, there were three 12-month open label studies.

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.The applicant has provided a statement to the effect that clinical trials conducted outside the

Table 1 Tabular overview of clinical studies

Study Number	Phase	Study Design	Study Objective	Subject Status/Patient Diagnosis	Number Exposed to HPN-100/ Control(s)
UP 1204-003	2	Non-randomized, open-label, fixed-sequence, switch-over	Safety and efficacy	Adult UCD (≥18 years)	10/14[a]
HPN-100-005	2	Non-randomized, open-label, fixed-sequence, switch-over (SO) followed by a long-term open-label safety extension (SE)	Safety and efficacy	Paediatric UCD (6 – 17 years)	SO: 11/11[a] SE: 17/-

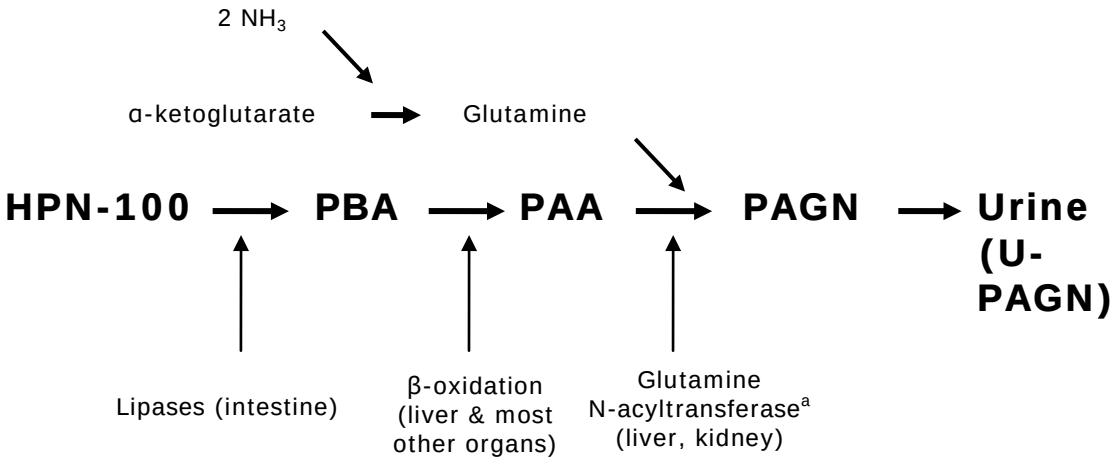
Study Number	Phase	Study Design	Study Objective	Subject Status/Patient Diagnosis	Number Exposed to HPN-100/ Control(s)
HPN-100-006	3	Randomized, double-blind, crossover	Safety and efficacy	Adult UCD (≥18 years)	44/45[a]
HPN-100-007[c]	3	Uncontrolled	Safety	Adult and paediatric UCD (≥6 years)	60/-
HPN-100-012	2	Non-randomized, open-label, fixed-sequence, SO followed by a long-term open-label SE	Safety and efficacy	Paediatric UCD (29 days to 5 years)	SO: 15/15[a] SE: 23/-[d]
HPN-100-011[e]	4	Uncontrolled continued access	Safety	Adult and Paediatric UCD (≥2 months)	88/-
UP 1204-001	1	Randomized, open-label, cross-over	PK	Healthy	24/24/24/24[f]
UP 1204-002	1	Uncontrolled	PK	Hepatic or healthy	32/-
HPN-100-008	2	Randomized, open-label, run-in (Part A) followed by randomized, double-blind (Part B)	Hepatic impairment	Hepatic	Part A: 15/- Part B: 90/88
HPN-100-010	1	Randomized, double-blind, crossover	Thorough QTc	Healthy	86/70/78[g]
HPN-100-019	2	Monosequence, open label, crossover	PK	Healthy	24

2.5.1. Pharmacokinetics

Absorption

Ravicti Glycerol phenylbutyrate (HPN-100) is a nitrogen-binding agent AND is a pro-drug of PBA. HPN-100 consists of three molecules of phenylbutyric acid (PBA) joined to glycerol by ester linkage to form a short-chain triglyceride, which appears to be digested by pancreatic lipases to release PBA (Studies Lowe 2009; A3091-11). Because the synthesis of each molecule of glutamine requires two nitrogen molecules, the body excretes two nitrogen molecules with each molecule of phenylacetylglutamine (PAGN). This is the same stoichiometry as for urea, each molecule of which also contains two nitrogen molecules. The biotransformation of HPN-100 is summarized in the following figure:

Biotransformation of HPN-100 (glycerol phenylbutyrate)



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

[a] This conversion likely involves more than one enzyme present in liver and kidney (Moldave 1957)

Upon oral ingestion, PBA is released from the glycerol backbone in the gastrointestinal tract by pancreatic lipases. PBA derived from RAVICTI is further converted by β-oxidation to PAA.

In healthy, fasting adult subjects receiving a single oral dose of 2.9 ml/m^2 of RAVICTI, peak plasma levels of PBA, PAA, and PAGN occurred at 2 h, 4 h, and 4 h, respectively. Upon single-dose administration of RAVICTI, plasma concentrations of PBA were quantifiable in 15 of 22 participants at the first sample time post dose (0.25 h). Mean maximum concentration (C_{max}) for PBA, PAA, and PAGN was 37.0 µg/ml, 14.9 µg/ml, and 30.2 µg/ml, respectively. In healthy subjects, intact glycerol phenylbutyrate was not detected in plasma.

In healthy subjects, the systemic exposure to PAA, PBA, and PAGN increased in a dose dependent manner. Following 4 ml of RAVICTI for 3 days (3 times a day [TID]), mean C_{max} and AUC were 66 µg/ml and 930 µg•h/ml for PBA and 28 µg/ml and 942 µg•h/ml for PAA, respectively. In the same study, following 6 ml of RAVICTI for 3 days (TID), mean C_{max} and AUC were 100µg/ml and 1400 µg•h/ml for PBA and 65 µg/ml and 2064 µg•h/ml for PAA, respectively.

In adult UCD patients receiving multiple doses of RAVICTI, maximum plasma concentrations at steady state (C_{maxss}) of PBA, PAA, and PAGN occurred at 8 h, 12 h, and 10 h, respectively, after the first dose in the day. Intact glycerol phenylbutyrate was not detectable in plasma in UCD patients.

Metabolism

Overall, plasma concentrations of PBA and its metabolites in adults generally displayed less fluctuation following HPN-100 as compared to NaPBA treatment. (see further information in the target population later in the report).

In studies involving a comparison of TID dosing with HPN-100 versus NaPBA, the fluctuation between minimum and maximum metabolite levels in plasma ($C_{min\text{-}ss}$ versus $C_{max\text{-}ss}$ and decreasing again to $C_{min\text{-}ss}$) was less pronounced in adult patients with UCDs after dosing TID with HPN-100 than with NaPBA.

These differences in plasma fluctuation are consistent with the conclusion that in adults, PBA delivered as HPN-100 is absorbed more slowly from the gastrointestinal tract than when delivered as NaPBA, presumably reflecting the time required for digestion of HPN-100 by pancreatic lipases. Slower absorption of PBA results in more sustained levels of the active downstream metabolites, PAA and PAGN. The results suggest further that despite differences in plasma metabolite levels with HPN-100 and NaPBA, the extent of PBA absorption as measured by U-PAGN is very similar for the two drugs. This disparity in plasma level and U-PAGN likely reflects the fact that PBA undergoes variable fractional conversion to PAA and PAGN during first-pass metabolism and prior to reaching the systemic circulation.

Food effect

The study results suggest that food intake may slightly reduce the absorption of HPN-100 but this may also reflect faster metabolism due to the presence of increased nitrogen levels following food. However, in the clinical development programme, HPN-100 has been administered with meals in each of the clinical trials and is expected to be administered with meals in clinical practice to mitigate post-prandial ammonia production. This approach is based on the rationale that it is the formation of PAGN from PAA and the amino acid glutamine that constitutes the nitrogen-scavenging step and the excretion of PAGN in urine that mediates waste nitrogen removal. As the effects of food intake shown in these studies appear to be small it is unlikely to be clinically significant.

Distribution

The binding was dependent on concentration for PBA and PAA, as shown by the higher levels of free fraction with increasing concentrations over the ranges investigated. This has an impact on the assessment of linearity of pharmacokinetics.

Elimination

Excretion of PAGN rids the body of waste nitrogen that UCD patients who genetically are unable to excrete in the form of urea. Elimination pathways are similar to that of NaPBA. However it is noted that only 70% of the administered drug is accounted for.

Dose proportionality and dose dependency

The non-linearity in the pharmacokinetics of PAA and the decreased protein binding with time suggests that dose escalations should be performed with caution. Multiple dose studies in healthy volunteers used a different dose regimen from that proposed in the clinical. However the profiles provided in patients and from the population analysis there does not appear to be any unexpected changes in the pharmacokinetics with time.

Pharmacokinetics in target population

Pharmacokinetics of RAVICTI in Adult Patients

- *Study UP 1204-003*

Absorption/exposure

In Study UP 1204-003, when HPN-100 was administered to adults with UCD, the systemic exposure (AUC_{0-24}) of PBA was 27% lower than that observed with NaPBA (540 versus 739 µg·h/mL,

respectively), whereas exposure levels of PAA (575 versus 596 µg·h/mL, respectively) and PAGN (1098 versus 1133 µg·h/mL, respectively) were very similar.

Mean peak (C_{max-ss}) plasma concentrations of PAA following HPN-100 therapy were 23.5% lower than those observed with NaPBA (i.e., 40.5 and 53.0 µg/mL, respectively), and minimum plasma concentrations (C_{min-ss}) of PAA following HPN-100 therapy were approximately 2-fold higher than those observed with NaPBA (i.e., 7.06 versus. 3.56 µg/mL).

Overall, in Study UP 1204-003 plasma concentrations of PAA following HPN-100 treatment displayed a lower fluctuation between peak and trough as compared to the NaPBA formulation. The mean % fluctuation in PBA concentrations following NaPBA was around 61% higher than that observed after HPN-100 therapy. For PAA, mean % fluctuation in PAA concentrations was around 13% higher following NaPBA as compared to HPN-100 therapy (956% versus 843%, respectively). The mean fluctuation in PAGN concentrations was around 17% lower following NaPBA as compared to HPN-100 therapy (952% versus 1145%, respectively).

All PK parameters of PAA were associated with very high inter-patient variability. This variability is in part due to the range of doses of NaPBA and HPN-100 (7 to 18 g equivalent PBA) that were administered in this study and reflects as well inter-individual differences in PAA to PAGN conversion rate. The U-PAGN0-24 following HPN-100 treatments was slightly lower (11% lower) than that observed for NaPBA.

- *Study HPN-100-006*

In Study HPN-100-006, mean systemic exposure of plasma PBA was also lower (15%) after HPN-100 compared with NaPBA treatment (433 versus 508 µg·h/mL, respectively), but the decrease was not significant. Mean systemic exposure to PAA was significantly lower, by approximately 25%, for HPN-100 versus NaPBA (447 versus 599 µg·h/mL), as was the mean PAA C_{max-ss} (38.5 versus 52.2 µg/mL). The highest individual PAA level in any patient during HPN-100 or NaPBA treatment was 178 and 213 µg/mL, respectively, well below the levels reported by Thibault (1994; 1995) to be associated with toxicity (499–1285 µg/mL).

The mean % fluctuation in PBA concentrations in plasma following NaPBA was around 38% higher than that observed after HPN-100 therapy. Mean % fluctuation in PAA concentrations was around 57% higher following NaPBA as compared to HPN-100 therapy (2150% versus 1368%, respectively). For PAGN, mean fluctuation in PAGN concentrations was around 63% higher following NaPBA as compared to HPN-100 therapy (1434% versus 881%, respectively). Overall, plasma concentrations of PBA and its metabolites generally displayed less fluctuation following the administration of HPN-100 as compared to NaPBA treatment.

In conclusion, the systemic exposure of PAGN following HPN-100 and NaPBA treatments among adult patients in Study UP 1204-003 (1098 and 1133 µg·h/mL, respectively) were very similar to HPN-100-006 values (1127 and 1252 µg·h/mL). In addition, the U $PAGN_{0-24}$ for patients on HPN-100 treatment was essentially identical to that of patients on NaPBA (mean excretion = 13.50 and 13.62 g, respectively). Based on results from the ANOVA, the geometric least-squares mean ratio for Ae was 101% and that for Fe was 97.7%, with the 90% confidence intervals around the least-squares mean ratios for both parameters completely contained within the 80–125% interval.

Although treatment with HPN-100 resulted in significantly lower systemic exposure when compared with that of PAA and PAGN than NaPBA and thus is considered not bioequivalent in plasma, it was bioequivalent to NaPBA in terms of U-PAGN, which represents the extent of absorption of PBA. While the total PAGN excretion was essentially the same for both drugs, less PAGN was excreted in urine

during the 12–24-h (overnight) period than during the 0–12-h period following NaPBA treatment while excretion of PAGN in urine was more evenly distributed over 24 h after treatment with HPN-100 (Figure 2.7.2-8).

Collectively, these findings indicate that in adults, PBA delivered in the form of HPN-100 is absorbed more slowly from the gastrointestinal tract when compared to NaPBA, presumably reflecting the time required for conversion of HPN-100 to PBA by intestinal lipases and possibly greater amount of conversion of PBA to PAA and PAGN before it reaches the systemic circulation. Slower absorption of PBA into the circulation results in more sustained levels of the active downstream metabolites PAA and PAGN.

Pharmacokinetics of RAVICTI in Paediatric Patients

- *Study HPN-100-005*

In paediatric study HPN-100-005, the exposure (AUC_{0-24} and C_{max-ss}) of the metabolites PBA, PAA, and PAGN in plasma was not significantly greater in paediatric patients (6–17 years of age) after dosing with HPN-100 compared to NaPBA. The results are contrary to those observed after dosing in adult patients, who demonstrated greater exposure of these metabolites after dosing with NaPBA versus HPN-100. In addition, exposure of PAA in paediatric patients was greater than that observed in adults after dosing with both treatments. However, the differences between PAA levels during dosing with NaPBA and HPN-100 were small relative to the inter-patient variability observed.

Comparative PAA exposure among paediatric patients during dosing with HPN-100 and NaPBA was further explored by Pop PK modeling and dosing simulations. In brief, the results of these analyses, along with the non-compartmental PK analyses in UCD patients ages 2 months through 5 years, indicate that PAA exposure is very similar during dosing of paediatric patients with NaPBA and HPN-100 and that the rate of conversion of PBA to PAA varies directly with BSA, a finding which explains the generally higher PAA levels among

- *Study HPN-100-012*

In paediatric study HPN-100-012 the mean systemic exposure (AUC_{0-24}) during dosing with HPN-100 and NaPBA was generally similar for the two drugs for PBA (255 vs. 483 µg•h/mL, respectively), PAA (1096 vs. 1458 µg•h/mL, respectively) and PAGN (1130 vs. 946 µg•h/mL, respectively), both among all patients and among the age subgroups (< 2 years and 2 to < 6 years).

The concentration of urinary PAGN, as well as the ratio of the concentrations of urinary PAGN to urinary creatinine, which corrects for any drug-related differences in urine volume, was higher during treatment with HPN-100 than with NaPBA and exhibited less variability.

Since patients received a wide range of HPN-100 doses, which corresponded to the PBA equivalent of their prescribed doses of NaPBA ranging from 0.7 g to 8 g, total systemic exposure (AUC_{0-24}) and maximum concentration (C_{max}) varied widely. Many samples, primarily fasting samples, had undetectable PBA or PAA; up to 75% for PBA and 46% for PAA after NaPBA treatment with fewer concentrations below the limit of quantitation (LOQ) after HPN-100 treatment. PAGN was measurable in nearly all samples. Even patients with the highest PBA and PAA levels had plasma samples with non-measurable or very low PBA and PAA levels, indicating a lack of accumulation of these metabolites in this population. The observed variability in plasma metabolites levels can be explained by high fluctuation index (calculated as a percentage as the difference between minimum plasma concentration (C_{min}) and C_{max} divided by C_{min} x 100), the wide range of doses administered and the wide range of ages and body size in the study population.

Patients under two years of age showed higher overall PAA exposure as reflected by higher AUC_{0-24} and C_{max} levels after treatment with both drugs as compared with older children. As with paediatric patients ages 6 through 17, the data among this group exhibited considerable variability. Of four patients in this age category, two patients showed similar patterns to the older children ages two to under six. However, two patients with the highest PAA values on NaPBA or HPN-100 were both under two years of age. The highest PAA value was seen in Patient 05-1209, a two month old ASS female receiving 2.728 g of PBA (8.28 g/m^2) in the form of NaPBA treatment. Due to difficulty obtaining venous access on Day 10, PK parameters could not be calculated for this patient after HPN-100 treatment. However, the one blood sample drawn on HPN-100 at the 24-hr time point showed lower PAA levels than the corresponding 24-hr value on NaPBA treatment. In one male patient of one year old with ASS deficiency the highest PAA values after HPN-100 with overall higher AUC_{0-24} and C_{max} on HPN-100 were observed. He received 7.344 g (13.11 g/m^2) of PBA as HPN-100 (the PBA equivalent of the maximum labelled dose for NaPBA).

Pharmacokinetic Comparisons between Adult and Paediatric UCD Patients

The metabolite exposure after either NaPBA or HPN-100 across age groups shows high levels of variability and high fluctuation indices. The mean exposure to PBA, the parent metabolite, and mean exposure to PAGN, the terminal metabolite, show no systematic variation across age groups, while PAA exposure tended to decrease with increasing age, a finding consistent with those from population PK modeling which indicate that the rate of clearance/metabolism of PAA varies directly with body size. While, systemic metabolite exposure, assessed as C_{max} or AUC, is generally similar for HPN-100 and NaPBA, the minimum concentration (C_{min-ss}) is generally higher for all metabolites in all age groups during HPN-100 treatment, a finding consistent with slower gastrointestinal absorption of PBA when administered orally as HPN-100.

In all studies involving a comparison of TID dosing with HPN-100 versus NaPBA, the fluctuation between minimum and maximum metabolite levels in plasma (C_{min-ss} versus C_{max-ss} and decreasing again to C_{min-ss}) was less pronounced in patients with UCDs after dosing TID with HPN-100 than with NaPBA. These results are consistent with slower input of PBA into the systemic circulation when delivered orally as HPN-100 versus NaPBA. Despite differences in plasma metabolite levels with HPN-100 and NaPBA, the extent of PBA absorption as measured by U-PAGN excretion is very similar for the two drugs, which likely reflects the fact that PBA undergoes variable fractional conversion to PAA and PAGN during first-pass metabolism and prior to reaching the systemic circulation.

Overall, the results from these studies demonstrated that HPN-100 is equivalent to NaPBA in terms of waste nitrogen scavenging, as reflected by the nearly identical urinary output of PAGN during treatment with the two drugs. The findings further suggest that the extent of PBA absorption is similar when given orally as HPN-100 versus NaPBA, based on similar U-PAGN output, but that the rate of PBA absorption is slower when given as HPN-100 versus NaPBA, based on lesser % fluctuation in plasma metabolite levels and more evenly spaced day–night output of U-PAGN with HPN-100 dosing. Finally, the results suggest that variable presystemic conversion of PBA to PAA and subsequently to PAGN explains the considerable variability during dosing with both drugs in the levels of plasma metabolites, particularly PBA, despite very similar output of U-PAGN. Because U- PAGN is an important marker of the pharmacologic ammonia-trapping properties of HPN-100 and NaPBA, whereas plasma concentrations of the metabolites are not, it follows that U-PAGN is a more useful biomarker for assessing compliance and dosing.

The Pop PK modeling corroborates with, and strengthens the principal conclusions drawn from the PK analyses from these individual UCD studies, including a similar extent but slower rate of PBA absorption when given orally as HPN-100 versus NaPBA and variable presystemic conversion of PBA to

PAA and PAGN during dosing with both drugs. The modelling and simulations also confirm the lower PAA values in adults during dosing with HPN-100 as compared with NaPBA, predict very similar PAA values for the two drugs in paediatric patients, and provide additional information relevant to proposed dosing based on PAA and U-PAGN.

Pharmacokinetics interaction studies

Drug–drug interaction is not expected for concomitantly administered drugs that are not themselves P450 substrates, such as dietary supplements commonly taken by UCD patients including arginine or citrulline. Because HPN-100 and its metabolites do not induce P450 enzymes, administration of HPN-100 is unlikely to attenuate the effect of concomitantly administered drugs that are substrates for P450 enzymes. However, because PBA and PAA do inhibit CYP enzymes, an exaggerated drug effect is theoretically possible for concomitantly administered drugs that are also P450 substrates. Therefore an in vivo drug interaction study to evaluate the effect of HPN-100 on the PK of a drug that is sensitive substrate of CYP3A4/5 (e.g., midazolam) was initiated in study HPN-100-019.

Study HPN-100-019 was open-label, monosequence crossover, drug-drug interaction study of RAVICTI and midazolam in 24 healthy male and female subjects.

All subjects received all treatments in a sequential order. Subjects received a single oral dose of 3 mg midazolam liquid on the morning of Day 1 following an approximate 10-hour fast and just prior to administration of breakfast. Subjects received oral doses of 4.4 g RAVICTI as a liquid 3 times a day on Days 2 to 5, doses were administered just prior to a standard meal with the first dose of each day following an approximate 10 hour fast from food. On Day 5, a single oral dose of 3 mg midazolam was coadministered with the morning dose of RAVICTI.

Blood samples for analysis of plasma concentrations of midazolam and its metabolite, 1' OH midazolam, were collected on Days 1 and 5, for 24 hours postdose.

The results of the HPN-100-019 study indicate that exposure to RAVICTI results in decreased systemic exposure to midazolam and increased exposure to the 1-hydroxy metabolite of midazolam which is consistent with an induction of CYP3A4 enzyme.

These findings are contrary to those anticipated based on the in vitro studies, which demonstrated significant inhibition of CYP3A4 by PBA and PAA and, instead, suggest that steady state dosing of RAVICTI results in mild CYP3A4 induction. Specifically, as compared with systemic midazolam exposure prior to HPN-100 dosing, analyses following HPN-100 dosing indicated decreased exposure to intact midazolam as well as the increased exposure to its hydroxy metabolite (Table 2).

Table 2: Statistical Comparisons of Plasma Midazolam Pharmacokinetic Parameters Following Administration of Midazolam with RAVICTI (Day 5) Versus Midazolam Alone (Day 1)

Pharmacokinetic Parameter	Geometric LS Means			
	Midazolam Alone (Reference)	Midazolam+RAVICTI (Test)	Ratio Test/Reference	90% CI
	Day 1	Day 5	%	%
$AUC_{0\text{-}inf}$ (ng*hr/mL)	66.958	46.210	69.01	65.29 - 72.95

Pharmacokinetic Parameter	Geometric LS Means			
	Midazolam Alone (Reference)	Midazolam+RAVICTI (Test)	Ratio Test/Reference	90% CI
	Day 1	Day 5	%	%
AUC_{0-t} (ng*hr/mL)	64.668	44.121	68.23	64.64 - 72.01
C_{max} (ng/mL)	16.776	12.459	74.27	66.50 - 82.93

Induction of CYP3A4, which catalyzes the hydroxylation of midazolam, would explain both the decreased exposure to intact midazolam as well as the increased exposure to its metabolite. In general, physicians prescribing RAVICTI along with any of the drugs would need to be alert to the possibility of accelerated metabolism and decreased drug effect. Among the possible pharmacological agents, only proton pump inhibitors, known to have a wide therapeutic margin, were used among greater than 10% of patients in the RAVICTI clinical trials.

While CYP3A4 is involved in the metabolism of a substantial fraction of currently used pharmacological agents, drug–drug interaction is not expected for concomitantly administered drugs that are not themselves CYP substrates, such as the dietary supplements arginine or citrulline. However, it is possible that HPN-100 and its metabolites may induce CYP enzymes and therefore attenuate the effect of concomitantly administered drugs that are substrates for CYP enzymes. This is adequately described in the SmPC.

2.5.2. Pharmacodynamics

Mechanism of action

Ravicti (HPN-100) is a prodrug of PBA and shares the same mechanism of action and metabolic pathway as NaPBA approved by the European Medicines Agency [EMA] as AMMONAPS® in 1999 but differ in terms of absence of sodium. It is hydrolyzed to glycerol and PBA in the gastrointestinal tract via pancreatic lipases. Because hydrolysis presumably only begins after HPN-100 exits the stomach and enters the proximal small intestine where it is exposed to pancreatic lipases, PBA delivered orally as HPN-100 enters the circulation about 75% more slowly than when delivered orally as NaPBA. Intact HPN-100 is not detected in the circulation of animals or humans.

Primary and Secondary pharmacology

PBA is converted via β-oxidation to phenylacetic acid (PAA), which is conjugated enzymatically with glutamine to form phenylacetylglutamine (PAGN), which is excreted in the urine and thereby mediates excretion of waste nitrogen (Moldave, 1957). Because glutamine contains two nitrogen atoms, excretion of one mol of PAGN results in removal of two moles of nitrogen, the same as when urea is excreted in urine. Not only does glutamine participate in this alternative pathway for elimination of waste nitrogen, but glutamine levels correlate with plasma ammonia levels and symptoms in UCD patients, and its intracellular accumulation in glial cells is believed to mediate cerebral oedema (Butterworth, 2009; Maestri, 1992; Tuchman, 2008).

Blood ammonia was the pharmacodynamics efficacy surrogate in each of the short term studies evaluating 24-hour AUC of ammonia concentration between RAVICTI and sodium phenylbutyrate at steady state. In the combined pooled analysis of these short-term studies, ammonia AUC_{0-24} h was

774.11 and 991.19 [(µmol/L)*hour] during treatment with RAVICTI and sodium phenylbutyrate, respectively (n = 80, ratio of geometric means 0.84; 95% confidence intervals 0.740, 0.949).

2.5.3. Discussion on clinical pharmacology

Ravicti (HPN-100) is a prodrug of PBA and shares the same mechanism of action and metabolic pathway as NaPBA. It is hydrolyzed to glycerol and PBA in the gastrointestinal tract via pancreatic lipases. Because hydrolysis presumably only begins after HPN-100 exits the stomach and enters the proximal small intestine where it is exposed to pancreatic lipases, PBA delivered orally as HPN-100 enters the circulation about 75% more slowly than when delivered orally as NaPBA. Intact HPN-100 is not detected in the circulation of animals or humans.

Although no formal studies have been performed, the pharmacodynamics of this class of compounds (HPN-100 & NaPBA) is well known. PBA is converted via β-oxidation to its active metabolite PAA (Kormanic, 2012), which is conjugated with glutamine to form phenylacetylglutamine (PAGN), which mediates waste nitrogen removal through urinary excretion.

The compound, although it largely shares the same mechanism of action as sodium phenylbutyrate (NaPBA) AMMONAPS®, differ in terms of absence of sodium. Its PK programme has been limited to only one or two formal studies. However, in consideration of the shared structural features with a known compound (NaPBA) and taking into account the nature of the disease condition, this is considered to be overall acceptable.

The observed reduction in blood ammonia is consistent with the expected therapeutic effects of the two compounds. The blood ammonia levels and urinary PAGN are therefore important determinants of treatment outcomes and reflect the patients' clinical response to RAVICTI, although the correlation between determinants and clinical outcomes does not appear to have been fully investigated in this case.

Overall, the plasma concentration–time profiles of HPN-100 and NaPBA are comparable in terms of the extent of exposure. However it is acknowledged that due to sustained release characteristics ofRavicti a better removal of waste nitrogen throughout the day is observed.

A relevant interaction with the concomitant food has been found to slightly reduce the absorption of HPN-100. The mechanism of has not been elucidated. However, in the clinical development programme, HPN-100 has been administered with meals in each of the clinical trials and is expected to be administered with meals in clinical practice to mitigate post-prandial ammonia production. As the effects of food intake shown in these studies appear to be small it is unlikely to be clinically significant although the company has not appeared to have explored whether the chosen approach is completely without any detrimental effect.

The applicant has submitted only one formal interaction study. Based on this and other findings including population PK, the potential for any interaction with other compounds appears to be relatively small. Nevertheless the mode of action of the compound could theoretically influence the absorption of other medicinal products administered concomitantly. This aspect has been adequately described in the SmPC.

2.5.4. Conclusions on clinical pharmacology

Despite some limitations due to the limited studies submitted, the CHMP considered the clinical pharmacology has been sufficiently investigated, taking into account the data available and the

knowledge of the already authorised as Ammonaps with which Ravicti shares the same mechanism of action.

2.6. Clinical efficacy

The applicant had previously received CHMP advice regarding the efficacy and safety evaluation measures contained in the development programme and this programme was found to be suitable for such an evaluation, and in accordance with the relevant CHMP guidelines in operation at the time.

2.6.1. Dose response study(ies)

No formal dose ranging study has been performed or reported in the literature regarding the use of glycerol phenylbutyrate in patients with urea cycle disorders. Considering the prevalence and rarity of the disease condition the absence of formal dose finding studies can be considered acceptable based on the discussion below.

The selection of RAVICTI (HPN-100) treatment dose was empirically derived based on the current sodium phenylbutyrate (NaPBA) SmPC dosing recommendations which in turn are based on the weight of the UCD patient. RAVICTI (HPN-100) dosing regimen in Clinical Trials is summarised in Table 2 below.

Table 2 RAVICTI (HPN-100) Dosing in Clinical Trials

Protocol Specified Doses		**Administered HPN-100 Doses in Clinical Trials**[(1)]			
NaPBA Dose Range	**HPN-100 PBA Equivalent Dose**		**g/day**	**mg/kg/day**	**g/m^2/day**
450–600 mg/kg/day (patients ≤ 20 kg)	428–570 mg/kg/day 0.389–0.518 mL/m^2/day	Mean (SD)	11.70 (5.892)	237.54 (114.210)	7.93 (2.978)
9.9–13.0 g/m^2/day (patients > 20 kg)	9.4–12.4 g/m^2/day 8.6–11.2 mL/m^2/day	Median	9.90	227.48	7.95
Maximum daily dose: 20 g	around 19 g (17.4 mL)	Range	1.0–34.3	15.2–578.1	0.7–15.4

Rationale for Dosing Based on Body Surface Area:

The current NaPBA SmPC recommends that dosing be based on weight for UCD patients weighing less than 20 kg (which corresponds to approximately 6 years of age) and on Body Surface area (BSA) for patients weighing 20 kg or above. Based on normal weight and height growth charts, BSA calculated using Mosteller's formula decreases in proportion to weight as children grow, such that dosing based on BSA relative to dosing based on weight ranges from approximately 20% greater at 2 months of age to approximately equal at 1 year to approximately 17% less at age 6, for which the normal (50 percentile) weight is approximately 20-kg.

Dosing in UCD patients must be individualized based on a variety of factors including UCD subtype, growth requirements, dietary protein intake, and the severity of that patient's urea synthetic defect (which varies even for patients with the same subtype). The proposed dose range for HPN-100 (4.5 mL/m^2 to 11.2 mL/m^2) based on BSA covers these variations in younger children.

The applicant BSA-based dosing of all ages down to 2 months is further supported by:

(a) the similarity of observed dosing normalized by BSA across paediatric (age groups <2, 2-5, 6-11 and 12-17 years old) and adult UCD patients enrolled in the clinical studies,

(b) the similarity of projected PAA levels based on simulated dosing at the upper end of the proposed maximum range for HPN-100 versus NaPBA and (c) the avoidance of an abrupt and 'artificial' 15-20% decrease in dose as patients reach 20 kg in weight and are transitioned from dosing based on weight to dosing based on BSA.

Rationale for Starting Dose:

To achieve satisfactory ammonia control as quickly as possible, it is important to recommend having a starting dose and not only a dose range. The proposed starting dose for HPN-100 corresponds to the median dose (rounded) used among the 100 UCD patients in the pooled safety analysis; i.e., 7.8 g/m^2 for adult patients, 7.9 g/m^2 for paediatric patients with a BSA of ≥ 1.3 m^2, and 9.6 g/m^2 for paediatric patients with a BSA of ≤ 1.3.

It is understood that this is a guideline and that individual patient considerations will be required. This needs to be clearly mentioned in the SmPC.

For example, patients being switched from NaPBA to HPN-100 would ordinarily be switched to the PBA equivalent dose, just as in the clinical trials. For patients initiating therapy, the dose of HPN-100 would be expected to be somewhat lower among adult heterozygous females with presumed significant residual urea synthetic capacity and potentially higher for patients with neonatal-onset disease, which generally corresponds to little or no residual synthetic capacity.

Rationale for Upper End of the Dose Range

The upper end of the proposed HPN-100 dose range is 12.4 g/m^2. This is the PBA equivalent of the upper end of the currently approved dose range for NaPBA.

The projected PAA exposure, assessed either as C_{max} or AUC_{0-24} with dosing of HPN-100 at the upper end of the maximum range (12.4 g/m^2/day), is generally similar to the highest levels observed among paediatric and adult patients in the applicant clinical trials and similar for HPN-100 and NaPBA.

Of importance, fewer than 5% of patients would be expected to be exposed to C_{max} values above 500 µg/mL that could theoretically be associated with reversible neurological AE. Moreover, analysis of data showed no relationship between PAA C_{max} and neurological AEs among the 80 patients who participated in short-term controlled studies (UP 1204-003, the switch-over part of HPN-100-005 and HPN-100–012, and HPN-100-006).

Rationale for Lower End of the Dose Range:

The lower end of the proposed range (5mg/m^2/day) is less than that currently recommended for NaPBA, however this is not based on any difference in behaviour between the two drugs.

Rather, it is based upon a more complete understanding of the UCD clinical spectrum than was available at the time of NaPBA approval in 1996 and on the recognition that UCD patients with residual urea synthetic capacity who may benefit from therapy, would need less drug than patients with no

residual capacity, which was by and large the population that Brusilow studied when formulating his dosing recommendations.

The proposed range is also based on the observed NaPBA dose range in clinical practice and, in fact, reflects the actual HPN-100 dose range employed among the UCD patients in the applicant studies, with exclusion of the lowest 25th percentile whose data were analysed for purposes of dosing in the Pop PK modelling. The proposed minimum dose for HPN-100 corresponds to the 25th percentile dose used among the adult UCD patients in the clinical trials (i.e., 5.32 g/m^2) and is very similar to that for all patients (5.31 g/m^2).

Rationale for Dose Adjustment and Monitoring

The recommendations for dose adjustment in the SmPC propose three approaches to therapeutic monitoring. One utilizes plasma ammonia, a mainstay for clinical management of UCD patients; one utilizes U-PAGN as a direct measure for waste nitrogen excretion and the last one utilizes plasma PAA levels and/or plasma PAA:PAGN ratio for assessment of potential toxicity when symptoms of vomiting, nausea, headache with somnolence, confusion or sleepiness are present in the absence of high ammonia. This is acceptable and adequately addressed in the SmPC.

2.6.2. Main studies

The clinical trials aimed at the demonstration of efficacy and safety as the primary objective are summarised in Table 3 below: These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

The clinical development programme comprised 6 of 7 UCD subtypes for which approval is sought.

Table 3a: Summary of RAVICTI (HPN-100 UCD) Efficacy Studies

Study Number	Phase	Study Design	Study Objective	Subject Status/Patient Diagnosis	Number Exposed to HPN-100/ Control(s)[a]
PIVOTAL					
HPN-100-006	3	Randomized, double-blind, crossover	Efficacy and Safety	Adult UCD ≥18 years	44/45[b]
SHORT-TERM SUPPORTIVE STUDIES					
UP 1204-003	2	Non-randomized, open-label, fixed-sequence, switch-over	Safety and efficacy	Adult UCD ≥18 years	10/14[c]
HPN-100-005	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Paediatric UCD ≥6 years - <18 years	11/11
HPN-100-012[f]	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Paediatric UCD ≥29 days - <6 years	15/15
LONG-TERM EFFICACY STUDIES					
HPN-100-007[d]	3	Uncontrolled	Safety	Adult and paediatric UCD	60/-
HPN-100-005 safety-extension[e]	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Paediatric UCD ≥6 years - <18 years	17/-
HPN-100-012 safety-extension[f,g]	2	Non-randomized, open-label, fixed-sequence, switch-over followed by a long-term open-label phase	Safety and efficacy	Paediatric UCD ≥29 days - <6 years	23/-

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

The comparative clinical efficacy of RAVICTI and sodium phenylbutyrate (NaPBA) was evaluated in 54 adult and 26 paediatric UCD patients who completed one of four short-term studies.

HPN-100-006 is considered to be the pivotal Phase 3 study in adults; HPN-100-005 and HPN-100-012, both a Phase 2 paediatric study; and UP 1204-003, a Phase 2 study in adults are all supportive.

Methods

HPN 100-006 was a Randomized, double-blind, crossover study to assess safety or efficacy of HPN-100 in adult patients with UCD.

***Study* Participants**

Adult patients with UCD

Treatments / Choice of Control Treatment

Placebo control was not feasible as any interruption of medication in patients with UCDs could lead to hyperammonaemic crisis and irreversible neurologic sequelae or death. Therefore, NaPBA was selected as the active-control in all studies.

NaPBA was administered orally three times daily (TID), with meals, as a 500-mg tablet (via mouth). Delivery via nasogastric or gastrostomy tube (G-tube) was permitted for patients who were unable to swallow. Patients who could not comply with taking NaPBA tablets were permitted to take NaPBA powder upon sponsor approval.

Objectives / Outcomes / endpoints

Primary endpoint

Blood ammonia, assessed as AUC_{0-24} at the end of each treatment period (Days 14 and 28), i.e., during steady-state dosing with HPN-100 or NaPBA, was selected as the primary efficacy endpoint in the pivotal efficacy study, HPN-100-006.

Secondary Endpoints

Maximum ammonia values observed on HPN-100 versus NaPBA, Rate (percentage) of ammonia values above the upper limit of normal (ULN) on HPN-100 versus NaPBA, Number and severity of symptomatic hyperammonaemic crises, Correlation between urinary PAGN (U-PAGN) excreted over 24 hours (U-PAGN0-24) and blood ammonia AUC_{0-24}, PK parameters including C_{max} for major urinary and plasma metabolites (PAA, PBA, and PAGN), Urinary PAA, PBA, PAGN levels

Post hoc efficacy analyses included the following:

Correlation of total dose administered with urine and plasma metabolites, Plasma ammonia AUC_{0-24} and maximum plasma concentration (C_{max}) by age at UCD onset (< 2 or ≥ 2 years of age), Glutamine levels on HPN-100 versus NaPBA.

Assessment of blood ammonia is central to the evaluation of efficacy and safety in UCDs, as it is the signature biochemical abnormality common to these disorders and believed to be a surrogate for outcomes. Control of blood ammonia is a primary objective of clinical management, and blood ammonia levels have been shown to correlate with clinical outcome.

The outcome of the CHMP & COMP Protocol Assistance was that this was regarded as a surrogate parameter; however; long term ammonia control has been clearly demonstrated in both the short term and long term studies. The timing of the ammonia measurements for measurement of AUC of blood ammonia was discussed and the overall analytical approach to assessing efficacy based on blood ammonia was agreed upon in the context of the Scientific Protocol Assistance. In the Phase 2 supportive efficacy studies, blood ammonia AUC_{0-24} on Day 7 and Day 14 was evaluated by post hoc efficacy analysis in adult UCD patients in UP 1204-003 and was pre-specified as an efficacy endpoint in paediatric UCD patients in HPN-100-005 and HPN-100-012.

Statistical methods

An ANOVA model for the natural log-transformed blood ammonia AUC_{0-24} was used to evaluate the non-inferiority of HPN-100 to NaPBA in controlling blood ammonia (as AUC_{0-24}) in the intent-to-treat (ITT) population. The 95% CIs of the treatment difference between the least squares mean (LSMs) (HPN-100 minus NaPBA) on the natural log scale were used to evaluate non-inferiority in the individual studies and after pooling the data across the three studies. Non-inferiority was concluded when the upper bound of the 95% CI was ≤ 1.25. Superiority was concluded when the upper bound of the 95% CI was < 1.0.

In Study HPN-100-006, the Hochberg procedure was employed to control the overall type I error rate (Hochberg, 1988) for the secondary efficacy analyses. No adjustments for multiple comparisons were made in UP 1204-003, HPN-100-005 or HPN-100-012.

In HPN-100-006 and HPN-100-005 missing ammonia data were imputed for patients who did not have a calculable blood ammonia AUC_{0-24} (< 12 h of ammonia data or patients missing both time 0 and 24 h values), or if the time 0 or time 24 h values were missing. In fact, very few ammonia samples were missed in either study, and little or no imputation was required. In HPN-100-012 each potential AUC was classified as either “incalculable” or “calculable”. An AUC was calculable if both 0 and 24 hr time points and at least one other time point (8 or 12 hr) was available; otherwise it was deemed as “incalculable” and no imputation of missing data was planned in the study. In UP 1204-003, missing data were imputed using the last-observation-carried-forward method for patients who had at least one blood ammonia 24 h AUC value after HPN-100 dosing

In Study HPN-100-006, the Hochberg procedure was employed to control the overall type I error rate (Hochberg, 1988) for the secondary efficacy analyses. No adjustments for multiple comparisons were made in UP 1204-003, HPN-100-005 or HPN-100-012.

Handling of Missing Data:

From the sequence of ammonia level concentrations, the AUC_{0-24} was calculated. However, if the ammonia level for any of the time points was missing, the calculation of the AUC_{0-24} was affected. Each potential AUC was classified as either “incalculable” or “calculable.” An AUC was “incalculable” if either of the following conditions applied to the ammonia level data: Both measurements from predose and 24 hours were missing.

The sampling interval was < 12 hours, e.g., the last available measurement was collected before the nominal 12-hour time point.

An AUC was “calculable” if neither of the above two conditions were met.

If a patient had both the AUC_{0-24} for HPN-100 and NaPBA as “incalculable,” then the patient was excluded from the analysis, e.g., AUC data were not imputed and AUC values were set to missing for both HPN-100 and NaPBA.

If an AUC was “calculable” but with some missing measurements, the following imputation was applied:

If either (not both) the predose or the 24-hour assessment was missing, then the predose or 24-hour assessment was imputed using the 24-hour and predose assessment, respectively. The nominal times of 0 hour and 24 hours were used for the imputed values of predose and 24-hour measurements, respectively.

No imputation was applied to missing measurements that occurred between predose and 24 hours exclusively. The calculation of AUC was based on available data. If an AUC was “incalculable,” then the following resampling approach was used for imputation:

The treatment (NaPBA or HPN-100) and dose level of the patient with the “incalculable” AUC was obtained.

Patients within ± 20% of the dose of the identified treatment in Step 1 were identified. If no patients were available, then all patients with the closest two doses were chosen.

Missing data were imputed by randomly selecting comparable data from patients in Step 2. The corresponding nominal times of the imputed values were used to impute the measurement times, which were needed in calculating the AUC.

After missing data were imputed as above, the actual collection times for available samples were used, and the trapezoidal rule was employed to calculate the AUC.

The proposed methods of analysis are acceptable. The results have been pooled for the Phase II and III studies and this approach is not supported. The results of the pivotal randomised Phase III study should be used as the main evidence to support this application. The non-inferiority margin of 1.25 was discussed in the CHMP scientific advice. It was considered that this margin was too wide and therefore for this single pivotal study to provide compelling evidence of non-inferiority it would be expected that the observed upper limit of the confidence interval will be well away from 1.25.

Overview across studies

Eligibility criteria and dosing as well as efficacy measures and analyses were similar across the studies; the main differences were patient ages (adults in HPN-100-006 and UP 1204-003 and paediatric patients in HPN-100-005 and HPN-100-012), method of treatment assignment (double-blind, randomized crossover versus open label fixed sequence), and duration of dosing with each study treatment (2 weeks in HPN-100-006, 1 week in HPN-100-005 HPN-100-012 and UP 1204-003).

In HPN-100-006, UCD subtypes were restricted to CPS, OTC, or ASS; i.e., those for which the active comparator, NaPBA, is approved, while all UCD subtypes were permitted in the Phase 2 and long-term studies (HPN-100-005 SE, HPN-100-007 and HPN-100-012 SE).

Each study included patients whose UCDs were well controlled on a stable dose of NaPBA before study entry. In each study, patients were administered study treatment (HPN-100 and NaPBA) orally with meals, TID, and were converted from NaPBA to the PBA-equivalent dose of HPN-100 using the same approach (i.e., for each patient, the HPN-100 dose was calculated from the prescribed NaPBA dose before study enrolment).

The persistence of efficacy of HPN-100 in controlling blood ammonia levels for up to one year was evaluated in 51 adult and 49 paediatric patients across the three similar uncontrolled open-label long-term studies: HPN-100-007, HPN-100-005 SE and HPN-100-012 SE.

Similarities in study design permitted pooling of the data for the comparative analyses of HPN-100 and NaPBA during the short-term controlled studies as well as pooling of data from the three open-label long-term periods during which only HPN-100 was administered.

Results

Efficacy Results from Study HPN-100-006

Primary Analysis of Non-inferiority on Blood Ammonia AUC_{0-24} values

Results of the non-inferiority analyses in the ITT, MITT, and PP populations are summarised in Table 3b below.

Table 3b: Non-Inferiority Analysis of Blood Ammonia AUC_{0-24} by Treatment (ITT, MITT and PP Populations)

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

Source: Table 14.2.1.1, Table 14.2.1.4, Table 14.2.1.5
ITT = intent-to-treat, MITT = modified intent-to-treat, PP = per protocol, SD = standard deviation
[a] Individual missing ammonia AUC data were imputed if values were missing at 0 or 24 h or the patient had < 12 h of blood ammonia data (see SAP Appendix 16.1.9.1).
[b] Results on original scale were obtained by exponentiating the corresponding log-transformed results.

The primary analysis to assess the non-inferiority of HPN-100 to NaPBA in controlling blood ammonia (assessed as AUC_{0-24} levels) was performed in the ITT population. An ANOVA model for the natural log-transformed blood ammonia AUC_{0-24} was constructed with factors for treatment, sequence, patient nested in a sequence as a random effect, and period. The 95% CI for the difference between the HPN-100 and NaPBA means (HPN-100 minus NaPBA) on the natural log scale were constructed. Missing ammonia level measurements were imputed as described in the SAP.

The pre specified primary objective of the study was met. In the ITT population, HPN-100 achieved non-inferiority to NaPBA as the upper bound of the 95% CI was 1.034, i.e., well below the predefined non-inferiority margin of 1.25.

Non-inferiority of HPN-100 to NaPBA in controlling blood ammonia (assessed as AUC_{0-24}) was also evaluated in the MITT and PP populations. As shown in Table 3b, a consistent treatment effect was seen, with HPN-100 shown to be non-inferior to NaPBA in controlling blood ammonia in the MITT

population (upper bound of the 95% CI of 1.024) and the PP population (upper bound of the 95% CI of 1.030).

Analysis performed across trials (pooled analyses and meta-analysis)

- **Efficacy endpoints measurements**

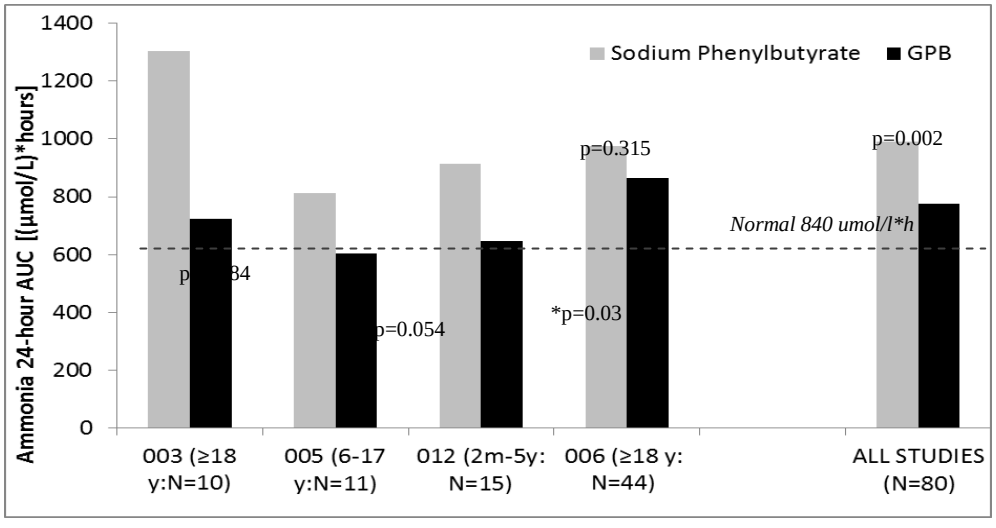
a) Effect on Blood Ammonia: AUC_{0-24} (Primary Efficacy Analysis)

A clinically meaningful and statistically robust difference in favour of HPN-100 versus NaPBA in controlling blood ammonia levels, as measured by AUC_{0-24} (774.11 vs. 991.19 µmol·h/L, respectively), was shown in the pooled analysis (Figure 1).

The mean difference between HPN-100 and NaPBA in the ITT population (n = 78) was -178.99 µmol·h/L (p = 0.004, paired t-test; p = 0.002, Wilcoxon signed-rank test). The upper bound of the 95% CI was 0.949. Results of sensitivity analyses on the primary efficacy endpoint were almost identical to the pooled analysis as the upper bound of the 95% CI was 0.945 when only including patients who had at least 4 blood ammonia samples (including the 8- or 12-hour samples) (n = 76) and when excluding the single patient with a randomization error (n = 77). Moreover, the 24-hour profile was similar among the four studies, with ammonia values consistently lower late afternoon and overnight during dosing with HPN-100.

Across these studies, mean blood ammonia AUC_{0-24} values for each treatment at steady state ranged from 602.17–865.85 µmol·h/L for HPN-100 and 813.48–1303.48 µmol·h/L for NaPBA. The non-inferiority of HPN-100 to NaPBA in controlling blood ammonia assessed as AUC_{0-24} was demonstrated in each study, with the upper bound of the 95% CI below the predefined non-inferiority margin of 1.25: 1.116 in Study UP 1204-003, 1.095 in Study HPN-100-005, 1.034 in Study HPN-100-006, and 1.055 in Study HPN-100-012.

Figure 1: Blood Ammonia AUC_{0-24} (ITT Population)



*Wilcoxon sign ranked test, p=0.03; T test, p=0.075
003 = Study UP 1204-003; 005 = Study HPN-100-005; 012 = Study HPN-100-012; 006 = Pivotal effficacy study HPN-100-006
AUC = area under the curve; GPB = glycerol phenylbutyrate; ITT = intent-to-treat; m = month; y = year.

b) Effect on Blood Ammonia: Maximum Blood Ammonia Values

Evidence of a treatment benefit of HPN-100 versus NaPBA in controlling maximum blood ammonia levels was similarly demonstrated in the pooled analysis of C_{max}, which was significantly lower in the ITT population by 12.29 ± 42.885 µmol/L during HPN-100 treatment compared with NaPBA treatment (p = 0.012, paired t-test; p = 0.030, Wilcoxon signed-rank test). Mean blood ammonia C_{max} values for the pooled analyses are summarized in Table 4 below.

Table 4: Blood Ammonia C_{max} in the Pooled Analysis (ITT)

	Blood Ammonia 24-h C_{max} (µmol/L)		
	NaPBA	**HPN-100**	**Difference Between HPN-100 and NaPBA**
n	82	80	80
Mean	69.51	55.73	-12.29
SD	58.513	39.675	42.885
Median	49.00	44.05	-3.10
Min	9.3	12.1	-184.4
Max	303.3	245.0	85.0
P-value[a]			0.012
P-value[b]			0.030

C_{max} = maximum plasma concentration; HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; Max = maximum; Min = minimum; NaPBA = sodium phenylbutyrate; OLFS = open-label fixed-sequence; SD = standard deviation.

Includes pooled data from UP 1204-003, HPN-100-005, HPN-100-006, and HPN-100-012.

[a] P-value obtained from a paired *t*-test comparing the difference between HPN-100 and NaPBA
[b] P-value obtained from a Wilcoxon signed-rank test comparing the difference between HPN-100 and NaPBA

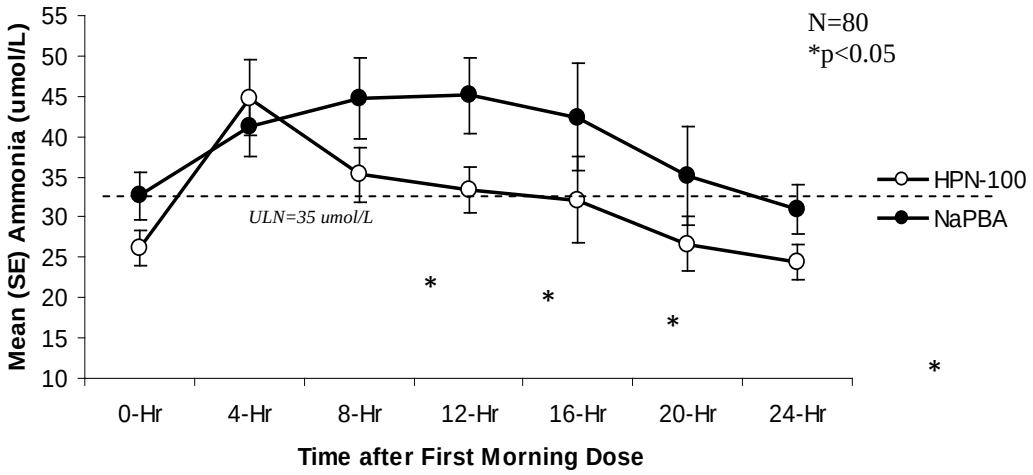
Mean blood ammonia C_{max} concentrations ranged from 39.39–66.21 µmol/L for HPN-100 and 52.74–98.40 µmol/L for NaPBA.

c) Effect on Blood Ammonia: Blood Ammonia Values over 24 Hours

The 24-hour blood ammonia pattern with HPN-100 treatment compared with NaPBA in the pooled analysis was consistent with the individual study results.

Post-prandial increases in mean blood ammonia levels were higher early in the day with HPN-100 (from 4 to 5 hours after dosing) and lower in the afternoon and overnight (from 6 to 12 hours after dosing) compared with NaPBA treatment. Mean 24-hour blood ammonia levels in the pooled analysis were lower on HPN-100 compared with NaPBA treatment at most time points (Figure 2). These differences in the 24-hour blood ammonia profile during dosing with HPN-100 versus NaPBA are explained by differences in the PK of the two study treatments.

Figure 2: Pooled Analysis: Mean Blood Ammonia over 24 hours After Treatment with NaPBA and HPN-100 (ITT Population)



*p<0.05 by Wilcoxon signed-rank test comparing the difference between HPN-100 and NaPBA

HPN-100 = glycerol phenylbutyrate; ITT = intent to treat; NaPBA = sodium phenylbutyrate; SE = standard error.

Average daily ammonia in the pooled analysis was significantly lower on HPN-100 versus NaPBA treatment: 31.20 ± 21.026 versus 38.29 ± 29.143 µmol/L (p = 0.008, paired t-test; p = 0.027, Wilcoxon signed-rank test). In all of the studies, daily average blood ammonia levels during steady-state treatment were within the normal range (35 µmol/L) with HPN-100 treatment (range: 23.91–34.71 µmol/L) and were slightly higher with NaPBA (range: 31.34–45.84 µmol/L).

d) Effect on Blood Ammonia: Blood Ammonia Values above ULN

The mean percentage of blood ammonia samples (per patient) with a value above the ULN was non-significantly lower with HPN-100 treatment than NaPBA treatment: 28% versus 37% of samples (Table 5). Similarly, in the pooled analysis, the percentage of all blood ammonia samples above the ULN at all time points was lower with HPN-100 treatment compared with NaPBA treatment: 30% (173/573 samples) versus 37% (219/592 samples), respectively.

Blood ammonia levels above the ULN across individual studies were similar to that of the pooled analysis. The mean percentage of blood ammonia samples above the ULN (per patient) was lower with HPN-100 treatment compared with NaPBA treatment in the open-label switch-over studies: 27% versus 43% in UP 1204-003, 18% versus 31% in HPN-100-005, and 13% versus 38% in HPN-100-012. None of the differences were statistically significant. The mean percentage of blood ammonia values above the ULN was similar in HPN-100-006: 36% (122/343) with HPN-100 versus 36% (125/345) with NaPBA. Similarly, the percentage of all blood ammonia samples above the ULN at steady state was lower after patients switched to HPN-100 treatment from NaPBA treatment: 29% of HPN-100 samples (29/101) versus 43% of NaPBA samples (48/113) in UP 1204-003, 18% (14/76) versus 32% (24/76) of samples in HPN-100-005, and 15% (8/53) versus 38% (22/58) of samples in HPN-100-012.

Table 5 Percentage of Blood Ammonia Samples above the ULN in the Pooled Analyses (ITT Population)

	NaPBA (N = 85)	HPN-100 (N = 85)	P-value[b]	P-value[c]
Percentage of Samples Above ULN[(1)]			0.098	0.110

	NaPBA (N = 85)	HPN-100 (N = 85)	P-value[b]	P-value[c]
n	82	80		
Mean (SD)	36.92 (35.863)	27.97 (32.496)		
Median	25.00	14.29		
Min, Max	0.0, 100.0	0.0, 100.0		

HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; NaPBA = sodium phenylbutyrate; SD = standard deviation; ULN = upper limit of normal; Min = minimum; Max = maximum.

Includes pooled data from UP 1204-003, HPN-100-005, HPN-100-006, and HPN-100-012.

(1) The percentage of samples above ULN is calculated for each patient using data from all time points at steady-state visits. After normalization, the ULN was 35 µmol/L.

b P-value was obtained from a two-sample t-test.

c P-value was obtained from a Wilcoxon rank-sum test.

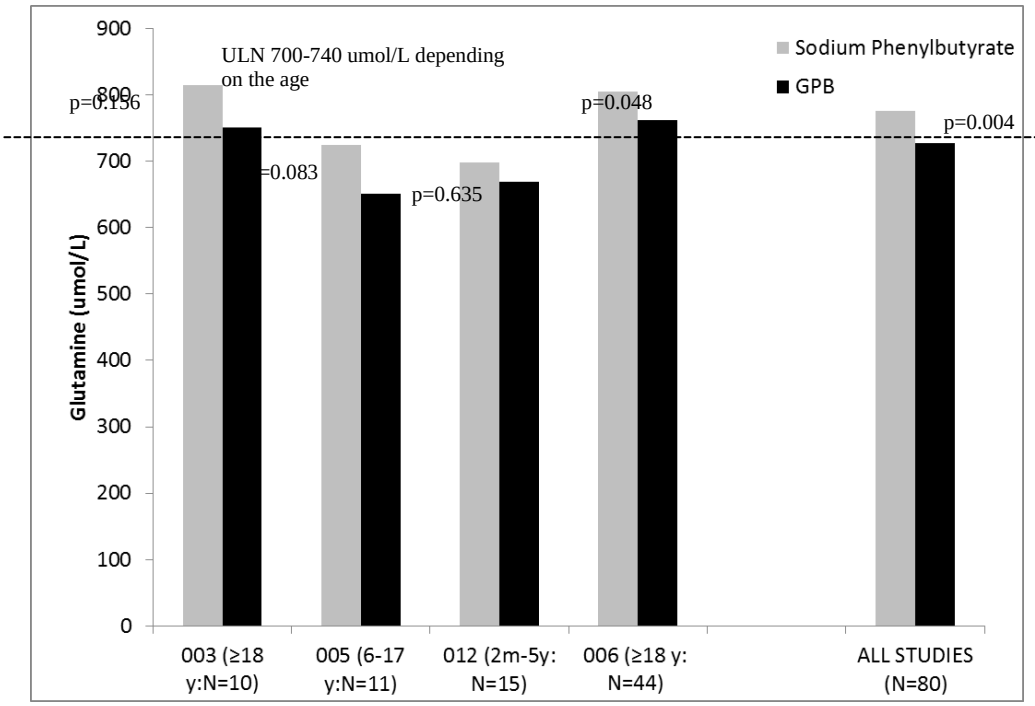
From the pooled analysis provided, the blood ammonia lowering capacity is superior for the HPN-100 group compared to the NaPBA group. However, it is not considered acceptable to make this claim in the SmPC and it is acceptable that the Applicant has not referred to the pooled analysis in the section 5.1 of the proposed SmPC.

e) Effect on Blood Glutamine

Blood glutamine levels have been shown to correlate with plasma ammonia levels and symptoms in UCD patients and are actively involved in the alternative pathway for elimination of waste nitrogen through combination with PAA to form PAGN (Maestri, 1992; Tuchman, 2008). Therefore, the relative effect of HPN-100 and NaPBA on blood glutamine levels was evaluated in each study. The mean difference between the study treatments in blood glutamine levels was analyzed using the paired t-test and the nonparametric Wilcoxon signed-rank test and are presented for the pooled analysis and across studies are presented in Figure 3.

Results of the pooled analysis provide further evidence that HPN-100 treatment lowers blood glutamine levels as effectively as with NaPBA treatment (Figure 3). Mean blood glutamine levels were significantly lower after HPN-100 treatment compared with NaPBA treatment by 50.4 ± 154.78 µmol/L (p = 0.006, paired t-test; p = 0.004, Wilcoxon signed-rank test). The significant decreases in blood glutamine were consistent with the significant decreases in blood ammonia AUC_{0-24} levels of 178.99 ± 525.964 µmol·h/L after HPN-100 treatment compared with NaPBA in the pooled analysis of the primary efficacy endpoint (p = 0.004, paired t-test; p = 0.002, Wilcoxon signed-rank). Slightly fewer patients had glutamine levels above 1000 µmol/L on HPN-100 (9 patients [12%]) compared with NaPBA (11 patients [14%]).

Figure 3: Mean Blood Glutamine Levels Across Studies (ITT Population)

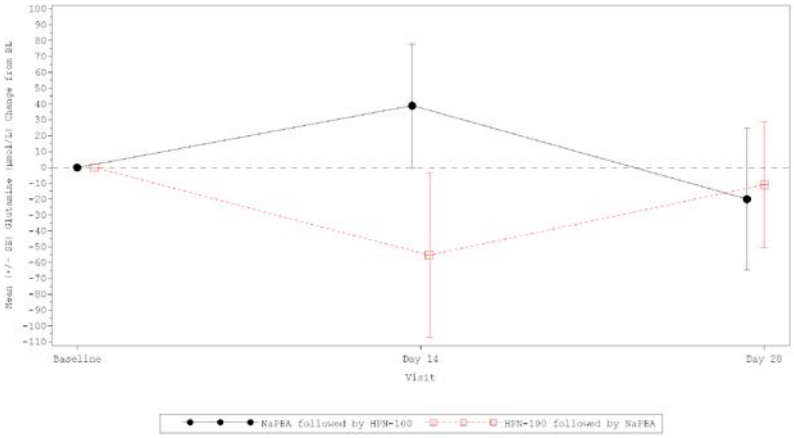


003 = Study UP 1204-003; 005 = Study HPN-100-005; 012 = Study HPN-100-012; 006 = Pivotal effficacy study HPN-100-006
GPB = glycerol phenylbutyrate; ITT = intent-to-treat; m = month; y = year.
Normal range 700-740 umol/L depending on the age.

In the open-label, fixed-sequence studies, mean blood glutamine levels on HPN-100 treatment were lower than on NaPBA treatment (decrease of 106.4 ± 205.34 µmol/L with HPN-100 treatment in UP 1204-003, 74.8 ± 134.95 µmol/L in HPN-100-005, and 20.1 ± 149.99 µmol/L in HPN-100-012), but the differences were not statistically significant.

In the pivotal Phase 3 study HPN-100-006, the treatment difference in blood glutamine values was nearly statistically significant (decrease of 44.3 ± 154.43 µmol/L after HPN-100 compared with NaPBA; p = 0.064, paired t-test; p = 0.048, Wilcoxon signed-rank test). Note that this statistical analysis differs from that in the HPN-100-006 CSR (-51.2 µmol/L; p = 0.031 paired t-test; p = 0.017 Wilcoxon signed-rank test), because the SAP for HPN-100-006 stipulated analysis based on treatment group assignment, whereas the SAP for the pooled analysis stipulated analysis based on treatment actually received, and 1 patient in HPN-100-006 (02-601) received the wrong treatment. Moreover, blood glutamine levels were lower with HPN-100 treatment than with NaPBA in each treatment period of the crossover study regardless of the treatment sequence (Figure 4). The bidirectional changes in glutamine relative to randomized treatment group assignment constitute persuasive evidence of a differential effect on glutamine of HPN-100 relative to NaPBA.

Figure 4: HPN-100-006: Mean Blood Glutamine Values During Each Treatment Period (ITT Population)



BL = baseline; HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; NaPBA = sodium phenylbutyrate; SE = standard error.

Note: Data for the 'HPN-100 followed by NaPBA' group are displaced slightly to the right to avoid overlap of the SE bars; baseline, Day 14, and Day 28 visits all occurred at the same time in both treatment arms.

f) Urinary PAGN Analyses

On the last day of treatment with HPN-100 and NaPBA (i.e., at steady state), U-PAGN0-24 was evaluated as a secondary efficacy analysis in Studies UP 1204-003, HPN-100-005, HPN-100-006, and in the pooled ISE analysis excluding HPN-100-012. U-PAGN0-24 was not assessed in HPN-100-012 because timed urine collections are not possible in young children without external or internal catheterization, which is not ethically justifiable. Instead, spot urine samples of PAGN and PAA were collected, allowing for measurement of PAGN and creatinine concentrations and the PAGN-to-creatinine ratio. Comparison of the PAGN-to-creatinine ratio was intended to correct for any spurious differences between the two drugs due to differences in, for example, urine volume, because of the higher salt content of NaPBA, which could result in greater urine output and lower PAGN concentration.

Mean urine PAGN concentration and urine-to-creatinine ratio were higher during treatment with HPN-100 than during treatment with NaPBA. Mean PAGN concentration was 13,544 mg/L during HPN-100 treatment versus 9665 mg/L with NaPBA, and PAGN-to-creatinine ratio was 27.6 g/g with HPN-100 versus 18.2 g/g with NaPBA. The results of the urine data analyses from HPN-100-012 demonstrated that urinary PAGN output was at least as high during dosing with HPN-100 compared with NaPBA and varied less over 24 hours, and are consistent with those in older paediatric patients ages 6–17 years (HPN-100-005) and adults (UP 1204-003 and HPN-100-006) as well as the findings from population PK modelling.

U-PAGN 0-24was evaluated on Day 7 and Day 14 in adult UCD patients in UP 1204-003 and in paediatric UCD patients ≥ 6 years of age in HPN-100-005. In the pivotal Phase 3 crossover study (HPN-100-006), U-$PAGN_{0-24}$ was evaluated on Days 14 and 28 in adult UCD patients. In addition to analysis of 24-hour excretion, U-PAGN excretion during the day (0–12 hours) and night (12–24 hours) was evaluated. In general, U-$PAGN_{0-24}$ = U-$PAGN_{0-12}$ + U-$PAGN_{12-24}$.

U $PAGN_{0-24}$ output was also summarized by treatment group, and the natural log-transformed value was analyzed using ANOVA. The ANOVA model included factors for treatment, sequence, subject nested in sequence (as a random effect), period, and study. The 95% CI for the difference between

HPN-100 and NaPBA means (HPN-100 minus NaPBA) on the natural-log scale was constructed using the least square means from the ANOVA model. The difference and lower and upper CI values were exponentiated to express the results as geometric means, ratio of geometric means, and corresponding CI on the original scale. The two treatment groups also were compared using the paired t-test and the nonparametric Wilcoxon signed-rank test.

Mean U-PAGN$_{0-24}$ excretion at steady state and treatment differences in pooled analysis are summarized in Table 6. The amount of U-PAG N0-24 excreted in the urine after HPN-100 treatment was nearly identical to the amount excreted after NaPBA treatment.

Across the studies, mean U-PAGN $_{0-24}$ hour excretion during steady-state treatment was very similar between the treatments and ranged from 10,960,292.73 µg to 14,050,389.39 µg with HPN-100 treatment, and from 11,793,116.71 µg to 14,182,358.15 µg with NaPBA treatment.

Table 6: Mean U-PAGN $_{0-24}$ in the Pooled Analysis (ITT Population)

U-PAGN$_{0-24}$ (µg)	Study Treatment		Difference Between HPN-100 and NaPBA
	NaPBA (N = 70)	HPN-100 (N = 70)	
n	64	65	64
Mean	13,522,019.64	13,312,791.74	-109,483.00
SD	7,168,017.020	7,313,207.399	4,041,640.967
Median	12,371,724.95	12,066,388.88	-196,901.72
Min	1,898,809.1	2,591,104.3	-8,405,394.4
Max	39,420,791.1	47,649,596.4	10,694,668.7
Ratio of geometric means[a]			1.01
P-value[b]			0.829
P-value[c]			0.776
90% CI[a]			(0.937, 1.080)
95% CI[a]			(0.924, 1.095)

CI = confidence interval; HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; NaPBA = sodium phenylbutyrate; Min = minimum; Max = maximum; SD = standard deviation; U-PAGN$_{0-24}$ = urinary phenylacetylglutamine excreted from 0–24 h.
Includes pooled data from UP 1204-003, HPN-100-005, and HPN-100-006. Timed urine data collections were not done in HPN-100-012 and thus U-PAGN$_{0-24}$ was not calculated. [a] Results on original scale were obtained by exponentiating the corresponding log-transformed results.
[b] P-value obtained from a paired t-test. [c] P-value obtained from a Wilcoxon signed-rank test

Maintenance of Long Term Efficacy

Long-Term Effect on Ammonia:

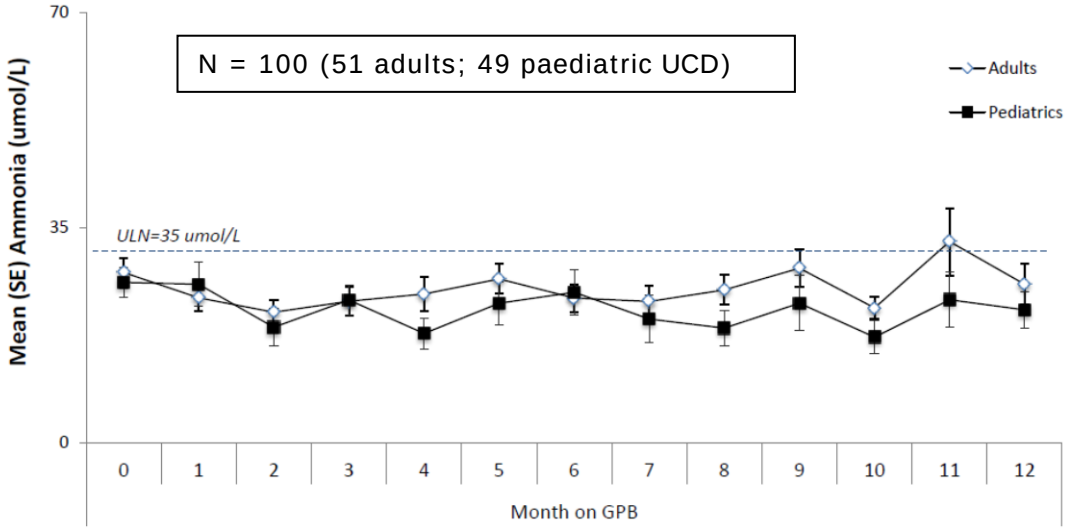
The long-term effect on ammonia was evaluated in 51 adult and 49 paediatric UCD patients treated with HPN-100 in the long-term open-label studies HPN-100-005 SE, HPN-100-012 SE, and HPN-100-007. Among patients undergoing long-term HPN-100 treatment, all UCD subtypes, with the exception of CITRIN and NAGS, are represented. The relative number of patients with each subtype corresponds with their relative prevalence, except that a greater number of patients with ASS and ASL deficiencies were enrolled in HPN-100-012, as these are the subtypes that are identified by newborn screening.

Over 12 months of treatment with HPN-100, mean ammonia values were within normal limits for both paediatric and adult patients at each monthly visit and overall were very similar to the mean fasting values (times 0 or 24 hours) observed during the short-term, switch-over studies (HPN-100-006, HPN-

100-005, HPN-100-012, and UP 1204-003). The mean ammonia ranged from 20.382 µmol/L (Month 10) to 29.593 µmol/L (Month 11) across 12 months of treatment with HPN-100.

These data collectively provide strong evidence that HPN-100 is effective in controlling ammonia for up to at least 12 months of treatment.

Figure 5: Long-Term Blood Ammonia Levels in Patients Treated with HPN-100



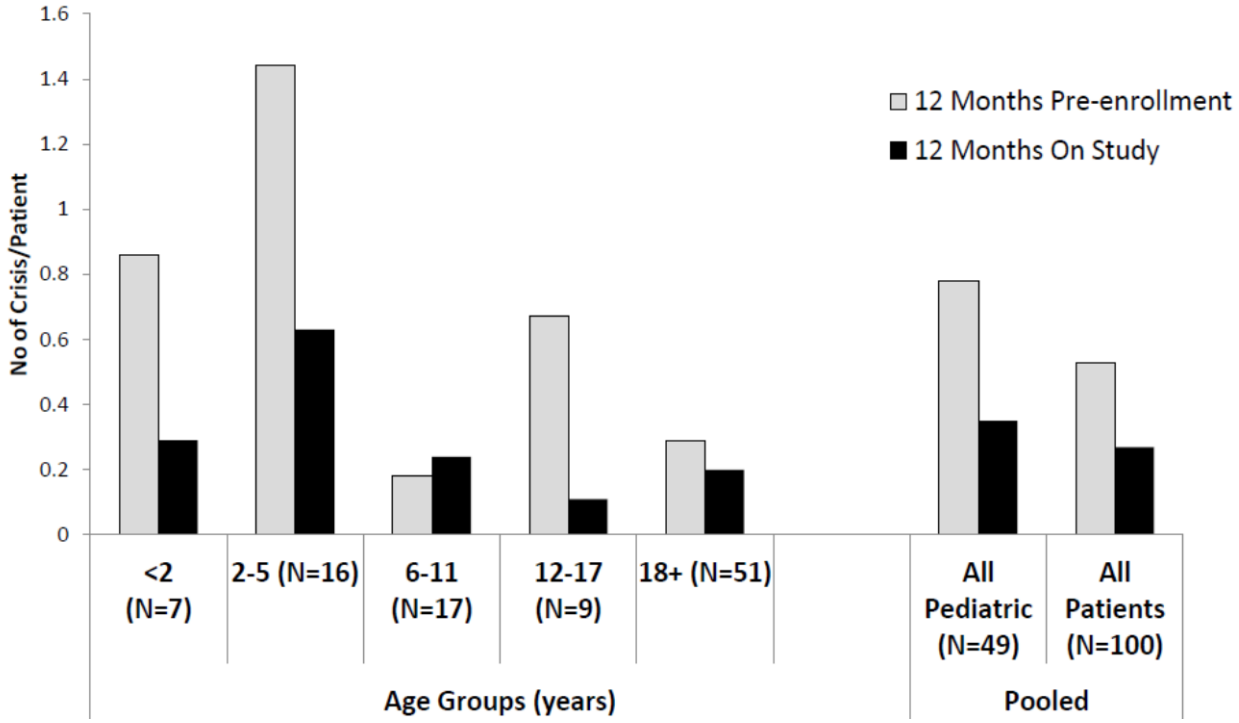
Ammonia values normalized to a reference range of 9-35 µmol/L. HPN-100 = glycerol phenylbutyrate; ITT = intent-to-treat; SE = standard error. **Note**: Mean upper limit of normal among participating sites around 35 µmol/L.

Long-Term Effect on Hyperammonaemic Crisis:

The rate of hyperammonaemic events per patient during the long-term safety studies HPN-100-005 SE, HPN-100-007 and HPN-100-012SE, is presented in Figure 6. Hyperammonaemic crises were most frequent in patients aged 2–5 years who are more susceptible to toxic effect of high ammonia, both in the 12 months preceding the studies (1.44/patient versus. 0.53/patient overall) and during long-term treatment with HPN-100 (0.63/patient versus. 0.27/patient overall).

Overall, 30 patients experienced a total of 53 hyperammonaemic events in the 12 months preceding enrolment in the HPN-100 studies, which represents on average 0.53 events per patient per year. With long-term treatment with HPN-100 in these studies, 19 patients experienced 27 hyperammonaemic crises, which represents on average 0.27 events per patient per year.

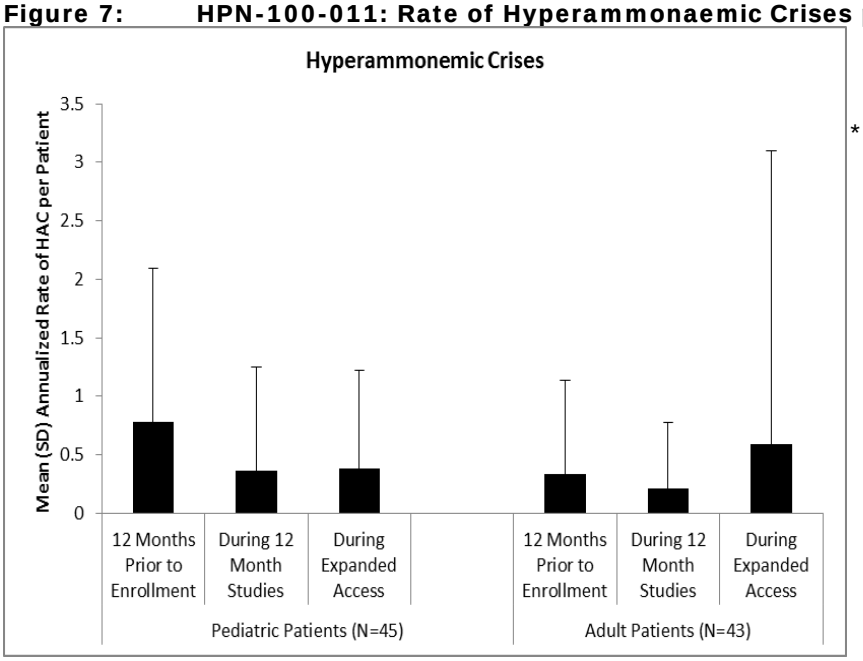
Figure 6: Rate of Hyperammonaemic Crisis per Patient (Safety Population)



HAC were recorded retrospectively for 12 months prior to enrolment. 30 patients had 53 HAC over the previous year on NaPBA. During HPN-100 treatment over 12months, 19 patients had 27 HAC over the year on GPB

When the rate of hyperammonaemic was evaluated in the 88 patients who continued to received HPN-100 through the continued access study (HPN-100-011; mean duration 552.0 days), where they were followed less frequently (i.e., per standard of care or every 6 months), the rate of HAC remained similar to the long-term studies (HPN-100-005 SE, HPN-100-007 and HPN-100-012SE). For paediatric patients the rate of crises decreased from 0.78 crisis per year during the 12 months preceding enrolment in Hyperion trials when the patients were being treated with NaPBA to 0.36 and 0.38 during 12-month controlled study and expanded access treatment with HPN-100, respectively, indicating the durability of the effect of HPN-100 during extended period of time in the most vulnerable group of patients (Figure 7).

Figure 7: HPN-100-011: Rate of Hyperammonaemic Crises per Patient



* Patient 05-7605 experienced 2 crises in 45 days on study in HPN-100-011 prior to study.

Clinical Relevance of the Observed Effects

The slower gastrointestinal absorption of PBA given orally (75%) as HPN-100 vs. NaPBA is associated with more even day-night distribution of urinary PAGN excretion and significantly lower ammonia levels (as reflected by the results of 80 patients ages 2 months to over 70 years who underwent 24 hour ammonia monitoring during steady state equivalent dosing of HPN-100 and NaPBA).

These lower ammonia levels were observed among all patient subgroups based on gender, age (paediatric vs. adult), UCD subtype (OTC vs. non-OTC) and age of onset, which is an indicator of severity. This excellent ammonia control was also maintained over 12 months of dosing in both adult and paediatric studies.

The clinical relevance of the ammonia control is reflected in improved long-term outcomes, including approximately 50% fewer total hyperammonaemic crises during 12 months of dosing with HPN-100 as compared with the prior 12 months during dosing with NaPBA and improved executive function among children ages 6 through 17.

The analysis of fasting ammonia in relation to both short term ammonia exposure and hyperammonaemic crises indicate that the fewer crises observed on HPN-100 is presumably a result of the better ammonia control, this is considered clinically relevant.

Clinical studies in special populations

No studies in special populations have been performed. However, the company has evaluated the results according to several post-hoc defined subgroups/criteria such as gender, age, race and subtype.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Summary of Study HPN-100-006

Title: Study to compare the treatment effects of Sodium phenylbutyrate (NaPBA) and Glycerol phenylbutyrate (HPN-100, Ravicti)				
Study identifier	HPN-100-006			
Design	Phase III, randomised, double-blind, cross-over, active-controlled study			
	Duration of Run-in phase:		4 weeks (2 weeks on each treatment)	
Hypothesis	Non-inferiority			
Treatments groups	Sodium phenylbutyrate (NaPBA) followed by Glycerol phenylbutyrate (formerly glyceryl tri-(4-phenylbutyrate (HPN-100, Ravicti)		For 4 weeks (2 weeks on each treatment) (n=22)	
	HPN-100 followed by NaPBA		For 4 weeks (2 weeks on each treatment (n=24 (note patient 20-630 withdrew on Day 1 after randomisation but before receiving any study treatment because of a failure to meet inclusion criterion 1 (blood ammonia level was 152 µmol/L) hence this patient is not included in any analysis)	
Endpoints and definitions	Primary endpoint	Blood ammonia (AUC_{0-24}) on Days 14 and 28		
	Secondary endpoint	Maximum blood ammonia values		
	Secondary endpoint	Rate (percentage) of blood ammonia values above the upper limit of normal (ULN) on NaPBA versus HPN-100		
	Secondary endpoint	Number of severity of symptomatic hyperammonemic crises		
	Secondary endpoint	Correlation between 24-h urinary PAGN excretion (U-$PAGN_{0-24}$) and blood ammonia AUC_{0-24}		
	PK and PD endpoints	PK parameters including C_{max} for major metabolites of NaPBA and HPN-100 (including plasma PAA, PBA, PAGN and U-$PAGN_{0-24}$)		
	Safety endpoint	Rate of adverse events in each treatment group		
Database lock	Study started 12 October 2009, Completed 9 September 2010, Database lock date not stated in study report. Database Unlock approval form signed 26 October 2010 (This was authorised to correct data entry errors identified after database lock and unblinding).			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (after 2 weeks of treatment)			
Descriptive statistics and estimate variability	Treatment group	NaPBA	HPN-100	Difference between HPN-100 and NaPBA
	Number of subjects	n=44	n=44	n=44

	Blood ammonia (AUC_{0-24}) Mean SD Median Min, Max Ratio of geometric means 90% Confidence Interval 95% Confidence Interval	 976.63 865.352 652.48 301.9, 4665.9	 865.85 660.529 672.59 206.0, 3351.1	 -111 579 -47 -2953,1007 0.91 (0.816, 1.012) (0.799, 1.034)
Analysis population and time point description	MITT (after 2 weeks of treatment)			
Descriptive statistics and estimate variability	Treatment group	NaPBA	HPN-100	Difference between HPN-100 and NaPBA
	Number of subjects	n= 43	n=43	n=43
	Blood ammonia (AUC_{0-24}) Mean SD Median Min, Max Ratio of geometric means 90% Confidence Interval 95% Confidence Interval	 985.61 873.517 674.18 301.9, 4665.9	 867.67 668.234 655.52 206.0, 3351.1	 -118 583.8 -74 -2953,1007 0.90 (0.807, 1.002) (0.789,1.024)
Analysis population and time point description	PP (after 2 weeks of treatment)			
Descriptive statistics and estimate variability	Treatment group	NaPBA	HPN-100	Difference between HPN-100 and NaPBA
	Number of subjects	n= 43	n=43	n=43
	Blood ammonia (AUC_{0-24}) Mean SD Median Min, Max Ratio of geometric means 90% Confidence Interval 95% Confidence Interval	 985.61 873.517 674.18 301.9, 4665.9	 868.29 668.145 655.52 206.0, 3351.1	 -117.18 584.224 -74.32 -2952.9,1006.6 0.90 (0.809, 1.007) (0.792,1.03)
	Safety			

	No hyperammonemic crises were reported with HPN-100 and no patients discontinued HPN-100 treatment because of a treatment emergent adverse event (TEAE). One patient had a treatment emergent serious adverse events (TESAE) of acute gastroenteritis while on HPN-100 that was attributed to food poisoning. In the NaPBA treatment arm, one patient had a TESAE of hperammonemic crisis that was related to noncompliance with diet, and one patient discontinued NaPBA treatment because of high blood ammonia levels (123 µmol/L) and headache on Day 1 of the study. 51.1% (23/45) of patients reported TEAEs while receiving NaPBA. 61.4% (27/44) of patients reported TEAEs while receiving HPN-100. Most TEAEs were considered by the investigator to be mild in intensity. Symptoms suggestive of lower GI disorders (diarrhoea and flatulence) were reported more frequently on HPN-100 treatment whereas symptoms suggestive of upper GI disorders (abdominal discomfort, dyspepsia, nausea and oral discomfort) were reported more frequently on NaPBA treatment.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of the clinical studies had previously been discussed and for the most part the applicant has conducted the trials in accordance with previous scientific advice received.

The applicant provided results from one pivotal study in adult patients with UCD and supportive studies in the paediatric population. The clinical programme comprised of 6 subtypes of UCD.

As study HPN-100-006 was the only randomized study this study is considered pivotal to this application.

Efficacy data and additional analyses

The results of the primary analysis of the pivotal study provide evidence of non-inferiority of HPN-100 to NaPBA in terms of levels of blood ammonia. Consistent results were seen for analyses of the mITT and PP populations. Only 2 subjects withdrew from the study; one withdrew on Day 1 before receiving any study medication because she had uncontrolled blood ammonia levels and patient 07-617 withdrew on Day 1 after receiving one dose of study drug (NaPBA) because of adverse events due to noncompliance with diet.

Based on individual studies and pooled analyses of all patients, as well as separate pooled analyses of all adult patients and all paediatric patients, HPN-100 has been shown to provide ammonia control that is comparable to NaPBA. In short term studies, a statistical difference in favour of HPN-100 versus NaPBA in controlling blood ammonia levels, as measured by AUC_{0-24} (774.11 versus 991.19 µmol·h/L, respectively), was shown in the pooled analysis of 80 patients, ages 2 months through over 70 years who underwent 24-hour ammonia monitoring during equivalent, steady state dosing of both drugs.

The lack of controlled long term study data is a limitation in the data provided considering the urea cycle disorders are chronic conditions which require long term treatment, hence the need for proper investigation during chronic administration. The applicant should therefore provide suitable long term study data during the post approval setting to further characterise long term use. Collection of the information will be done through the disease registry for 10 years.

Notwithstanding, the database for long term continuous treatment in open label studies provides further information on RAVICTI when administered chronically, although with limitations due to the open design.

Comments overall across studies

Overall, the use of both RAVICTI and NaPBA offer a benefit across the majority of the efficacy outcome measures. In particular, efficacy was demonstrated in the reduction for both blood ammonia and glutamine.

There were no significant differences between treatment groups either patients who received RAVICTI and those who received the active comparator, NaPBA. However, it is acknowledged that the sustained release characteristics provided a better control during the day allowing nitrogen waste removal to occur more evenly. 17.

The analysis of fasting ammonia in relation to both short term ammonia exposure and hyperammonaemic crises indicate that the fewer crises observed on HPN-100 is presumably a result of the better ammonia control. In the long term studies, the clinical relevance of the ammonia control is reflected in improved long-term outcomes, including approximately 50% fewer total hyperammonaemic crises during 12 months of dosing with HPN-100 as compared with the prior 12 months during dosing with NaPBA and improved executive function among children ages 6 and above.

As with the other efficacy measurement outcomes discussed above, across the studies, the mean urinary $PAGN_{0-24}$ excretion was similar between the two (HPN-100 and NaPBA) treatment groups.

There were no apparent differences in response to the study medication between the different subgroups. More importantly, the numbers of the subgroups are quite small for any meaningful interpretation of the results.

As only 6 of 7 UCD subtypes for which approval is sought have actually been investigated, the CHMP considered that there was no sufficient justification for the inclusion of the subtype of citrullinaemia deficiency in the indication.

Assessment of paediatric data on clinical efficacy

The pivotal and supportive clinical studies provided in the application included paediatric patients from the 2 months of age.

Despite the limited number of patients this is considered acceptable to support an indication in paediatric patients from 2 months of age.

The total daily dose should be individually adjusted according to the patient's protein tolerance and the daily protein intake needed to promote growth and development.

The applicant demonstrated the possibility of using nasogastric tube or gastrostomy tube administration if oral administration would be difficult in very young patients. This is adequately addressed in the SmPC.

2.6.4. Conclusions on the clinical efficacy

Overall, the efficacy data generated from the clinical evaluation programme suggest that RAVICTI is effective in treatment of patients with urea cycle disorders (UCDs) as demonstrated by the results of the controlled short term studies. The efficacy has been demonstrated in the following subgroups of patients older than 2 months and suffering from UCD: 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.

2.7. Clinical safety

The overall safety evaluation of RAVICTI (HPN-100) consisted of pooled analyses in three different populations for which clinical studies involving HPN-100 were conducted as follows: studies conducted in Urea Cycle Disorder (UCD) patients (target population); studies conducted in healthy volunteers (HV); and studies conducted in patients with hepatic impairment (HI). This safety summary focuses primarily on the pooled analysis in the UCD target population, with some reference to the analyses conducted in the HV and HI population, as applicable.

The safety evaluation of HPN-100 in the target UCD population included a pooled analysis of the four short-term controlled studies (UP 1204-003, HPN-100-005, HPN-100-006, and HPN-100-012) and a separate pooled analysis of three 12-month open-label safety studies (HPN-100-005 safety-extension [SE], HPN 100-012 SE, and HPN-100-007). Collectively, these studies enrolled 121 UCD patients, of which 114 received at least one dose of HPN-100.

Patient exposure

A total of 359 patients/subjects have received at least one dose of HPN-100, 114 of who were UCD patients, as part of the clinical development programme.

In the pooled analyses, 85 UCD patients (59 adults, 26 paediatric patients) received at least one dose of HPN-100 or NaPBA in the short-term controlled studies. A total of 100 UCD patients (51 adults, 49 paediatric patients) enrolled in one of the long-term open-label studies, including 66 patients who had completed one of the short-term controlled studies and 34 newly enrolled patients.

The mean total daily dose of HPN-100 was around 11 g in the short-term controlled and long-term open-label studies. Paediatric patients tended to receive larger mean total daily doses per kg of body weight or BSA than adult patients in the short-term controlled studies (HPN-100: 9.88 g/m^2/d versus 7.45 g/m^2/d, respectively; NaPBA: 10.19 g/m^2/d versus 7.73 g/m^2/d, respectively).

The median duration of exposure to HPN-100 was 51 weeks and 90 patients completed the long-term (12 month) open-label safety studies, of whom 88 enrolled into the continued access protocol (HPN-100-011) to continue receiving HPN-100 until commercialization. The mean duration of treatment during HPN-100-011 was 552.9 days (range: 0–957 days), and the mean total duration of treatment in all HPN-100 studies (i.e., including the previous study HPN-100-005SE, HPN-100-007, or HPN-100-012SE) was 916.2 days (range: 349–1318 days).

Since US approval in February 2013, 70 of the HPN-100-011 patients transitioned to RAVICTI, (note that six Canadian patients continue to receive HPN-100 under HPN-100-011) bringing the total during exposure in some patients to more than four years.

Adverse events

Serious adverse event / deaths / other significant events

For the purposes of the pooled analysis, the applicant has defined the incidence of common treatment-emergent adverse event (TEAEs) as TEAEs occurring in ≥ 10% of patients or subjects. These are presented in Table 7 for the pivotal study HPN-100-006 and the pooled short-term controlled safety analysis and the pooled long-term safety studies.

Table 7 Common Treatment-Emergent Adverse Events Reported in ≥ 10% of Patients from Any Treatment Group (Safety Population)

System Organ Class Preferred Term[c]	Short-Term Controlled Studies				Long-Term Open-Label Studies[b]
	HPN-100-006 Placebo Controlled		Pooled Safety Analysis[a]		
	NaPBA (N = 45)	HPN-100 (N = 44)	NaPBA (N = 85)	HPN-100 (N = 80)	HPN-100 (N = 100)
Any TEAE	23 (51.1)	27 (61.4)	33 (38.8)	43 (53.8)	98 (98.0)
Gastrointestinal disorders	13 (28.9)	16 (36.4)	18 (21.2)	24 (30.0)	57 (57.0)
Diarrhoea	3 (6.7)	7 (15.9)	4 (4.7)	7 (8.8)	18 (18.0)
Flatulence	1 (2.2)	6 (13.6)	1 (1.2)	8 (10.0)	3 (3.0)
Nausea	3 (6.7)	1 (2.3)	7 (8.2)	1 (1.3)	15 (15.0)
Vomiting	2 (4.4)	3 (6.8)	3 (3.5)	6 (7.5)	35 (35.0)
Nervous system disorders	7 (15.6)	7 (15.9)	11 (12.9)	8 (10.0)	37 (37.0)
Headache	4 (8.9)	6 (13.6)	4 (4.7)	7 (8.8)	12 (12.0)
Metabolism and nutrition disorders	4 (8.9)	3 (6.8)	7 (8.2)	6 (7.5)	38 (38.0)
Hyperammonaemia	1 (2)	0	2 (2.4)	0	19 (19.0)
Decreased appetite	2 (4.4)	3 (6.8)	3 (3.5)	3 (3.8)	13 (13.0)
General disorders and administration site conditions	2 (4.4)	5 (11.4)	3 (3.5)	6 (7.5)	29 (29.0)
Pyrexia	0	1 (2.3)	0	1 (1.3)	15 (15.0)
Infections and infestations	2 (4.4)	3 (6.8)	3 (3.5)	5 (6.3)	69 (69.0)
Upper respiratory tract infection	0	1 (2.3)	0	2 (2.5)	37 (37.0)
Nasopharyngitis	0	1 (2.3)	0	1 (1.3)	13 (13.0)
Respiratory, thoracic, and mediastinal disorders	0	1 (2.3)	0	3 (3.8)	33 (33.0)
Cough	0	1 (2.3)	0	2 (2.5)	16 (16.0)

Short-Term Controlled Studies:

During short-term controlled studies (UP 1204-003, HPN-100-005, HPN-100-006 and HPN-100-012) 53.8% (43/80) and 38.8% (33/85) of patients taking HPN-100 and NaPBA, respectively, experienced at least one TEAE. There were no deaths. No patient discontinued from HPN-100 treatment due to a TEAE, while 2 patients discontinued from NaPBA treatment because of high ammonia levels. Most TEAEs were considered by the investigator to be mild in severity and only one patient on HPN-100 and 2 patients on NaPBA had a severe TEAE. Treatment-related TEAEs were reported in 33.8% and 25.9% of patients on HPN-100 or NaPBA treatment, respectively. The safety profile in the pooled analysis of the short-term controlled studies is similar to that in the short-term, double blind double dummy, pivotal crossover study HPN-100-006.

The only TEAE occurring at a rate of ≥ 10% with HPN-100 treatment in the pooled short-term analysis was flatulence (10.0%). The most common TEAE during short-term treatment with NaPBA was nausea (8.2%). The most frequently reported treatment-related TEAEs reported by patients taking HPN-100 included diarrhoea, and headache (7 [8.8%] for each).

A larger proportion of adult than paediatric patients reported TEAEs with both HPN-100 (61.1% versus 38.5%, respectively) and NaPBA (52.5% versus 7.7%, respectively) during the short-term controlled studies, although the duration of treatment differed across the studies from 10 days in paediatric patients ages 29 days to 5 years (1 day of NaPBA followed by 9 days of HPN-100 in HPN-100-012), 2 weeks (1 week of NaPBA followed by 1 week of HPN-100) in adults and paediatric patients ages 6 to 17 years (UP 1204-003 and HPN-100-005), and 4 weeks (2 weeks of HPN-100 and 2 weeks of NaPBA) in adults (HPN-100-006).

Less common TEAEs were defined as those occurring in < 10%, but that occurred in more than 1 adult or more than 1 paediatric patient. Less common treatment-related TEAEs (Table 10) occurring with HPN-100 treatment included diarrhoea, flatulence, and headache each in 7 patients (8.8%); abdominal pain, fatigue, and increased appetite each in 3 patients (3.8%); and abdominal distension, upper abdominal pain, and dyspepsia each in 2 patients (2.5%). Less common treatment-related TEAEs occurring with NaPBA treatment included dyspepsia in 5 patients (5.9%); nausea in 4 patients (4.7%); decreased appetite, increased appetite, and food aversion each in 3 patients (3.5%); and abdominal discomfort, diarrhoea, gastroesophageal reflux disease, oral discomfort, dizziness, headache, and skin odor abnormal each in 2 patients (2.4%).

Long-Term Safety Studies:
While most patients (98.0%) in the open-label HPN-100 extension studies [HPN-100-005 SE, HPN-00-007 and HPN-00-012 SE] reported at least one TEAE, only 5 (5.0%) patients discontinued study treatment due to a TEAE. No deaths or life-threatening TEAEs were reported. Most of the TEAEs were mild or moderate in severity; 20.0% of patients had a severe TEAE.

Common TEAEs reported during long-term open-label treatment with HPN-100 included upper respiratory tract infection (37%), vomiting (35%), hyperammonaemia (19%), diarrhoea (16%), nausea and pyrexia (15% each), nasopharyngitis and decreased appetite (13% each) and headache (12%).

TEAEs were reported by a slightly greater proportion of adult than paediatric patients during long-term open-label treatment with HPN-100 (100% and 95.9%, respectively).

TEAEs that were notably more frequent in paediatric patients included pyrexia (22.4% paediatric, 7.8% adult), hyperammonaemia (24.5% paediatric, 13.7% adult), and streptococcal pharyngitis (10.2% paediatric, no adult). TEAEs that were notably more frequent in adults included nausea (21.6% adult, 8.2% paediatric), fatigue (11.8% adult, 4.1% paediatric), dizziness (15.7% adult, 2.0% paediatric), and oropharyngeal pain (13.7% adult, 2.0% paediatric).

Serious adverse events and deaths

Treatment-Emergent Serious Adverse Events (TESAEs) for the short term controlled studies and long term open-label studies in UCD patients are summarized in Table 8 below.

Table 8 Treatment-Emergent Serious Adverse Events in the Short Term Controlled and Long-Term Open-Label UCD Studies (Safety Population)

System Organ Class Preferred Term[c]	Number (%) of Patients		
	Short-Term Controlled Studies[a]		Long-Term Open-Label Studies[b]
	NaPBA (N = 85)	HPN-100 (N = 80)	HPN-100 (N = 100)
Any TESAE	2 (2.4)	1 (1.3)	26 (26.0)
Gastrointestinal disorders	0	0	3 (3.0)
Abdominal pain	0	0	1 (1.0)
Vomiting	0	0	2 (2.0)
Infections and infestations	0	1 (1.3)	4 (4.0)
Gastroenteritis	0	1 (1.3)	3 (3.0)
Lobar pneumonia	0	0	1 (1.0)
Injury, poisoning and procedural complications	0	0	1 (1.0)
Chemical burn of skin	0	0	1 (1.0)
Metabolism and nutrition disorders	2 (2.4)	0	20 (20.0)
Hyperammonaemia	2 (2.4)	0	18 (18.0)
Hypophagia	0	0	2 (2.0)
Nervous system disorders	0	0	3 (3.0)
Convulsion	0	0	2 (2.0)

System Organ Class Preferred Term[c]	Number (%) of Patients		
	Short-Term Controlled Studies[a]		Long-Term Open-Label Studies[b]
	NaPBA (N = 85)	HPN-100 (N = 80)	HPN-100 (N = 100)
Dizziness	0	0	1 (1.0)
Neuropathy peripheral	0	0	1 (1.0)
Psychiatric disorders	0	0	2 (2.0)
Aggression	0	0	1 (1.0)
Psychotic disorder	0	0	1 (1.0)
Reproductive system and breast disorders	0	0	1 (1.0)
Pelvic pain	0	0	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (1.0)
Lung infiltration	0	0	1 (1.0)

There were no deaths. During short-term controlled studies, three of 85 UCD patients (3.5%) reported a treatment-emergent serious adverse event (TESAE) in the short-term controlled studies. One patient (20-639) had a TESAE of acute gastroenteritis while on HPN-100 treatment, and 2 patients (06-608, 03-001/03-004) had a TESAE of hyperammonaemia on NaPBA treatment.

TESAEs were reported in 26 of 100 patients (26.0%) in the long-term open-label studies. None of the TESAEs occurring during the long-term open-label studies was considered by the investigator to be related to HPN-100 treatment. The most common TESAE was hyperammonaemia, which was reported in 18 patients. Other TESAEs included gastroenteritis in 3 patients; vomiting, hypophagia, and convulsion in 2 patients each; and the following in 1 patient each: abdominal pain, aggression, chemical burn of skin, dizziness, lobar pneumonia, lung infiltration, peripheral neuropathy, psychotic disorder, and pelvic pain in 1 patient each.

Eighty-eight UCD patients from the long-term safety extension studies enrolled in the continued access study, HPN-100-011, which is currently ongoing for 6 Canadian patients. As of 19 February 2014, no patient has died. Thirty patients have experienced TESAEs. The only TESAEs that were reported in more than 1 patient were hyperammonaemia (21 patients [23.9%]), abdominal pain (3 patients [3.4%]), and dehydration (2 patients [2.3%]).

Adverse Event in Population Subgroups

Differences in common TEAEs based on demographic factors and baseline characteristics were analysed using pooled data from the short-term controlled studies (UP 1204-003, HPN-100-005, HPN-100-006, HPN-100-012) separately from the long-term open-label studies (HPN-100-005 SE, HPN-100-007, HPN-100-012 SE) using the following demographic factors and baseline characteristics: age (29 days–< 2 years, 2–5 years, 6–11 years, 12–17 years, or ≥ 18 years); sex (male or female); race (white or non-white); UCD type (OTC or non-OTC); and age at onset of UCD (neonatal or infantile [birth to ≤ 2 years] or childhood or adult [> 2 years]).

Analysis by Age: TEAEs—In the short-term controlled studies, a smaller proportion of paediatric than adult patients reported a TEAE with HPN-100 and NaPBA treatments. HPN-100: 38.5% of paediatric versus 61.1% of adult patients. NaPBA: 7.7% of paediatric versus 52.5% of adult patients. The only TEAEs reported in paediatric patients with HPN-100 in the short-term controlled studies that were not also reported in adult patients were lymphadenopathy, ear infection, cardiac murmur, and papular rash in 1 patient each.

In the long-term open-label studies, a similar percentage of adult and paediatric patients reported a TEAE with HPN-100 treatment regardless of relationship to treatment (95.9% of paediatric versus 100.0% of adult patients). TEAEs reported in more than one paediatric patient that were not reported

in adult patients in the long-term open-label studies included pharyngitis streptococcal (5 [10.2%]), ear infection (3 [6.1%]), aggression (2 [4.1%]), anion gap increased (2 [4.1%]), blood alkaline phosphatase increased (2 [4.1%]), dermatitis (2 [4.1%]), lymphadenopathy (2 [4.1%]), gastroesophageal reflux disease (2 [4.1%]), hypokalaemia (2 [4.1%]), hypophagia (2 [4.1%]), hyporeflexia anion gap increased (2 [4.1%]), neutropenia (2 [4.1%]), and viral infection (2 [4.1%]).

Analysis by Gender: TEAEs— In the short-term controlled studies, a similar percentage of male and female patients reported a TEAE with HPN-100 and NaPBA treatments. HPN-100: 42.3% of male and 59.3% of female patients. NaPBA: 32.1% of male and 42.1% of female patients. In the long-term open-label studies, a similar percentage of male versus female patients reported a TEAE with HPN-100 treatment (97.0% of male and 98.5% of female patients).

Analysis by Race: TEAEs— In the short-term controlled studies, a higher proportion of white than non-white patients reported a TEAE with HPN-100 treatment whereas a lower percentage of white than non-white patients reported a TEAE with NaPBA treatment. HPN-100: 54.8% of white versus 50.0% of non-white patients. NaPBA: 35.4% of white versus 50.0% of non-white patients. In the long-term open-label studies, a similar percentage of white versus non-white patients reported a TEAE with HPN-100 treatment (97.5% of white and 100% of non-white patients).

Analysis by UCD Type: TEAEs— In the short-term controlled studies, a similar percentage of patients with OTC versus non-OTC deficiency reported a TEAE with HPN-100 treatment whereas a larger percentage of patients who had OTC deficiency compared with non-OTC deficiency reported a TEAE with NaPBA treatment. HPN-100: 55.0% of OTC and 50.0% of non-OTC. NaPBA: 42.2% of OTC versus 28.6% of non-OTC. In the long-term open-label studies, a similar percentage of OTC versus non-OTC patients reported a TEAE with HPN-100 treatment (98.6% of OTC and 96.8% of non-OTC).

Analysis by Age of Onset of UCD: TEAEs— In the short-term controlled studies, a smaller percentage of patients diagnosed with UCD at ≤ 2 years of age versus patients diagnosed at > 2 years reported a TEAE with either HPN-100 or NaPBA treatments. HPN-100: 44.1% of patients diagnosed ≤ 2 years versus 60.9% diagnosed > 2 years. NaPBA: 22.9% of patients diagnosed ≤ 2 years versus 50.0% diagnosed > 2 years. In the long-term open-label studies, a similar percentage of patients diagnosed ≤ 2 years and patients diagnosed > 2 years reported a TEAE with HPN-100 treatment (95.9% of patients diagnosed ≤ 2 years and 100% diagnosed > 2 years).

Adverse Events in Relation to Duration of Treatment

The proportion of patients with new-onset TEAEs decreased during long-term use of HPN-100; TEAEs were reported by 77.0%, 68.4%, 57.0%, 71.4%, and 38.5% of patients treated from 0 to 3; 3 to less than 6; 6 to less than 9; 9 to less than 12; and greater than or equal to 12 months, respectively. Similarly adverse events designated as related to study drug decreased from 33% during the first 3 months to 9.2% to 7.7% in subsequent quarters. Common TEAEs were more frequently reported during the first 3 months of HPN-100 treatment than at later time periods. While the incidence of the most common TEAEs tended to decrease with longer exposure, the incidence of respiratory tract infection, hyperammonaemia, headache, and diarrhoea generally remained steady over the 12 months of HPN-100 exposure.

There was no increase in the number of patients who experienced a TESAE with long-term HPN-100 exposure or who discontinued from treatment because of a TEAE with long-term exposure to HPN-100. Fifteen patients experienced a TESAE, and only two patients discontinued from treatment due to a TEAE during the long-term open-label period.

Laboratory findings

No relevant influence of RAVICTI was found on laboratory parameters such as blood cell parameters, and clinical chemistry, including parameters related to electrolyte, water, and bicarbonate balance. Although some clinically relevant changes could be found, these were deemed not significant and not related to the study medication.

The evaluation of vital signs, and ECGs did not reveal any abnormalities. The ECG evaluation also comprised a formal QTc study whose results were negative.

Liver Function

No clinically significant changes from baseline in biochemical liver tests were observed with either HPN-100 or NaPBA. Mean changes in liver function parameters from baseline to end of treatment were largely similar between NaPBA and HPN-100.

Safety in special populations

Please refer to discussion above under sub groups

Safety related to drug-drug interactions and other interactions

The results of in vitro analyses of the effects of HPN-100 and its reactive metabolites indicate that PBA and PAA do not result in significant induction of cytochrome P450 (CYP) enzymes commonly involved in drug metabolism. There was minimal induction of CYP3A4/5 by either PBA (<31% relative potency) or PAA (<19% relative potency) not considered enzyme inducers per 2006 Food and Drug Administration (FDA) guidelines. Since HPN-100 was insoluble in aqueous solutions, it was therefore not possible to test for induction in vitro in human hepatocytes (CFU0004). By contrast, an in vitro analysis of the effect of HPN-100 and its metabolites PBA and PAA demonstrated that PBA and PAA, but not HPN-100, were reversible inhibitors (>40%) of human CYP enzymes.

PBA was found to be a reversible inhibitor of CYP2C9, CYP2D6, and CYP3A4/5. The inhibitor constants (Ki) calculated for CYP2C9 and CYP2D6 were 1.3 mM and 1.5 mM, respectively (approximately 0.2 mg/mL for both). PAA is a reversible inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The Ki calculated for CYP2C9 was 15.1 mM (approximately 2.056 mg/mL).

Drug–drug interaction is not expected for concomitantly administered drugs that are not themselves P450 substrates, such as dietary supplements commonly taken by UCD patients including arginine or citrulline. Because HPN-100 and its metabolites do not induce P450 enzymes, administration of HPN-100 is unlikely to attenuate the effect of concomitantly administered drugs that are substrates for P450 enzymes. However, because PBA and PAA do inhibit CYP enzymes, an exaggerated drug effect is theoretically possible for concomitantly administered drugs that are also P450 substrates. Therefore an in vivo drug interaction study to evaluate the effect of HPN-100 on the PK of a drug that is sensitive substrate of CYP3A4/5 (e.g., midazolam) was initiated in January 2014 as part of post marketing commitment for US approval of RAVICTI (Protocol HPN-100-019).

Results from Study HPN-100-019 described earlier in the PK section, indicate that exposure to RAVICTI results in decreased systemic exposure to midazolam and increased exposure to the 1-hydroxy metabolite of midazolam which is consistent with an induction of CYP3A4 enzyme. These findings are contrary to those anticipated based on the in vitro studies, which demonstrated significant inhibition of CYP3A4 by PBA and PAA and, instead, suggest that steady state dosing of RAVICTI results in mild CYP3A4 induction. Specifically, as compared with systemic midazolam exposure prior to HPN-100

dosing, analyses following HPN-100 dosing indicated decreased exposure to intact midazolam as well as the increased exposure to its hydroxy metabolite.

A clinically significant drug–drug interaction is most likely to occur with administration of drugs that are both CYP substrates and exhibit a narrow therapeutic range, and the dose of such drugs must be titrated accordingly if co-administered with HPN-100 or NaPBA. However, none of the medications concomitantly prescribed in >10% of the 100 UCD patients in the long-term open-label studies (citrulline, amino acids, other nutrients, ibuprofen, multivitamin, paracetamol, amoxicillin, ondansetron, ergocalciferol, calcium, and loratadine)) or other potentially commonly used drugs in this population (non-steroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin reuptake inhibitors, and drugs for treating attention deficit–hyperactivity disorder) have a narrow therapeutic range, and no AEs were reported that could be attributed to high levels of such co-administered drugs.

Other Potential Drug Interactions

The concomitant use of drugs known to cause hyperammonaemia (such as valproate) or increase protein catabolism (such as corticosteroids), and drugs that significantly affect renal clearance (such as probenecid) were prohibited in the clinical studies of patients with UCDs studies. Caution should be used when administering corticosteroids, probenecid, haloperidol, or valproate with HPN-100

Discontinuation due to adverse events

TEAEs leading to early discontinuation of study treatment in the pooled analysis from the short term controlled studies and long-term open-label studies are summarized in Table 15. Also discussed in this section are TEAEs leading to early discontinuation of study treatment in the ongoing continued access study (Treatment Protocol HPN-100-011) in UCD patients.

Short-Term Controlled Studies: No patient discontinued from HPN-100 treatment because of a TEAE in the short term controlled studies. Two patients discontinued from NaPBA treatment because of a TEAE: one because of high blood ammonia levels (123 µmol/L) and headache and one because of severe hyperammonaemia.

Long-Term Open-Label Studies: Five patients (5.0%) had TEAEs that led to temporary or permanent withdrawal from study treatment in the long-term open-label studies. No AE preferred term led to study drug withdrawal in more than 1 patient.

Three of the 5 patients had study drug held or withdrawn for TEAEs considered related to study treatment and consistent with the known toxicity profile of HPN-100. All 3 patients had dose reductions. Two of these patients were newly enrolled in the safety extension, were not being treated with NaPBA at the time of enrolment, and experienced improvement in their symptoms following dose reductions of 50% during the first month of treatment. One patient subsequently completed the study, while the other patient remained on study for an additional 3 months on the reduced dose before withdrawing consent. One had a small dose reduction (from 18 to 16 mL/day) at Month 2 of treatment, but was withdrawn for AEs after 2 months of treatment at the reduced dose level. From the remaining 2 patients, one withdrew due to an TESAE of unspecified psychosis, intercurrent illness unrelated to study drug), and then withdrew consent for reasons unrelated to toxicity (study participation required travel too difficult to maintain), and the other patient (3 months old at study entry) withdrew for hyperammonaemia during the third month of treatment.

Continued Access Protocol HPN-100-011 — Of the 88 patients who had enrolled in the continued access study HPN-100-011 as of 19 February 2014, 2 patients had TEAEs leading to temporary

discontinuation of study treatment (one patient (pancreatitis) and one patient (hypocapnia)). Both were SAEs. The pancreatitis was considered unrelated to study drug and the hypocapnia was considered possibly related.

Table 10: Treatment-Emergent Adverse Events Leading to Discontinuation from Study Treatment in UCD Studies (Safety Population)

System Organ Class Preferred Term[c]	Number (%) of Patients		
	Short-Term Controlled Studies		Long-Term Open-Label Studies
	NaPBA (N = 85)	HPN-100 (N = 80)	HPN-100 (N = 100)
Any discontinuations due to TEAE	2 (2.4)	0	5 (5.0)
Gastrointestinal disorders	0	0	2 (2.0)
Abdominal distension	0	0	1 (1.0)
Flatulence	0	0	1 (1.0)
Nausea	0	0	1 (1.0)
Retching	0	0	1 (1.0)
Vomiting	0	0	1 (1.0)
General disorders and administration site conditions	0	0	2 (2.0)
Face oedema	0	0	1 (1.0)
Oedema peripheral	0	0	1 (1.0)
Infections and infestations	0	0	1 (1.0)
Urinary tract infection	0	0	1 (1.0)
Investigations	1 (1.2)	0	0
Ammonia increased	1 (1.2)	0	0
Metabolism and nutrition disorders	1 (1.2)	0	2 (2.0)
Decreased appetite	0	0	1 (1.0)
Hyperammonaemia	1 (1.2)	0	1 (1.0)
Musculoskeletal and connective tissue disorders	0	0	1 (1.0)
Back pain	0	0	1 (1.0)
Nervous system disorders	1 (1.2)	0	3 (3.0)
Dysgeusia	0	0	1 (1.0)
Headache	1 (1.2)	0	0
Lethargy	0	0	1 (1.0)
Paraesthesia	0	0	1 (1.0)
Speech disorder	0	0	1 (1.0)
Tremor	0	0	1 (1.0)
Psychiatric disorders	0	0	1 (1.0)
Psychotic disorder	0	0	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (1.0)
Dysphonia	0	0	1 (1.0)
Skin and subcutaneous tissue disorders	0	0	1 (1.0)
Rash	0	0	1 (1.0)
Skin odour abnormal	0	0	1 (1.0)

2.7.1. Discussion on clinical safety

The clinical safety database of UCD patients treated with HPN-100 over short and long term safety extension studies is reasonable and includes representation of 6 out of the 7 subtypes for which approval is sought.

Overall HPN-100 is shown to be well tolerated. TEAEs reported by patients during HPN-100 treatment in short term studies were generally similar both in frequency and type to those reported by patients during NaPBA treatment.

Most events were generally mild and there were no deaths or life-threatening TEAEs. The severity and nature of the adverse events tended to decrease with continued exposure.

Similarly, no clinically significant HPN-100 treatment–associated laboratory abnormalities have been observed. Several patients have had increased AST and or ALT; however, these were mostly attributable to concomitantly administered medications and/or liver test abnormalities known to be associated with the underlying UCD (Nagamani 2012; Gallagher 2014).

Analysis of shift tables indicates an overall effect on transaminase levels, with no differences between HPN-100 and NaPBA during comparative short-term studies.

In short term controlled studies, several (8) patients on NaPBA and none on HPN-100 discontinued treatment due adverse events. Given the relatively small number of patients and the lack of controlled data in long-term studies, no definite conclusions can be drawn on discontinuation due to adverse events.

The incidences of adverse events were similar across the population subgroups including gender' race or UCD subtype and there was no trend toward an increase in the incidence of any TEAE with long-term exposure with study medications.

Seemingly, a larger proportion of patients developed serious adverse events in open label studies even when taking into account the longer duration of exposure the study medication. Although due to lack of controlled data in long-term studies, no definite conclusions can be drawn on the occurrence of these serious adverse events in the long term studies.

Overall, the most frequently reported adverse reactions were diarrhoea, flatulence, headache (8.8%), decreased appetite (7%), vomiting (6.1%), fatigue, nausea and abnormal skin odour (5.3%).

The safety data show that HPN-100 have minimal effects on the hepatic function. However, the converse is not the case since conversion of PAA to PAGN occurs in the liver. In which case patients with hepatic impairment would be expected to have reduced conversion capability and higher plasma PAA and plasma PAA to PAGN ratio. Therefore, dosage for patients with mild, moderate to severe hepatic would need to be reduced. It is recommended to start at the lower range of the recommended dose. This is appropriately described in the SmPC (posology section).

Assessment of paediatric data on clinical safety

In the safety pooled analyses of UCD patients, 26 paediatric patients received at least one dose of HPN-100 or NaPBA in the short-term controlled studies. A total of 49 UCD paediatric patients were enrolled in one of the long-term open-label studies.

In the short-term controlled studies, a smaller proportion of paediatric than adult patients reported a TEAE with HPN-100 and NaPBA treatments.

HPN-100: 38.5% of paediatric versus 61.1% of adult patients. NaPBA: 7.7% of paediatric versus 52.5% of adult patients.

The only TEAEs reported in paediatric patients with HPN-100 in the short-term controlled studies that were not also reported in adult patients were lymphadenopathy, ear infection, cardiac murmur, and papular rash in 1 patient each.

In the long-term open-label studies, a similar percentage of adult and paediatric patients reported a TEAE with HPN-100 treatment regardless of relationship to treatment (95.9% of paediatric versus 100.0% of adult patients). TEAEs reported in more than one paediatric patient that were not reported in adult patients in the long-term open-label studies included pharyngitis streptococcal, ear infection, aggression, anion gap increased, blood alkaline phosphatase increased, dermatitis, lymphadenopathy, gastroesophageal reflux disease, hypokalemia , hypophagia, hyporeflexia anion gap increased, neutropenia and viral infection.

2.7.2. Conclusions on the clinical safety

Generally, the safety profile of RAVICTI appears to be acceptable and seems to be overall well tolerated. The safety database is appropriate for both adults and paediatric populations although the duration of the long term studies remains limited. However, considering the rarity of the disease, this is acceptable in support of an approval. The Company is proposing a disease registry. This will enable long term collection of safety data especially in young paediatric patients over 10 years to further characterise the safety profile of Ravicti. The CHMP agrees to have this registry as a condition to the marketing authorisation.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 could be acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice with minor changes.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Gastrointestinal Effects

Important potential risks	Toxicity due to the active metabolite PAA (Phenylacetic acid) Drug-Drug Interactions Use in patients with hepatic impairment Overdose Carcinogenicity Impaired Fertility Off-label use Reduced phenylbutyrate absorption in pancreatic insufficiency or intestinal malabsorption
Missing information	Use in patients with renal impairment Exposure during pregnancy and lactation Use in pre-term newborns and neonates Use in the elderly ≥ 65 years Use in UCD subtype NAGS deficiency Long term safety Use in UCD subtype CITRIN deficiency

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
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) (Clinical Study: HPN-100-009)[a] Category: 3	To evaluate PK, safety, efficacy, of GPB in children from birth to less than 2 months of age with UCD with an extension phase until the age of 24 months.	Safety and Other Endpoints • Rate of hyperammonaemic crises during the first 6 months on RAVICTI • Rate of AEs • Amino acid profile including glutamine, glutamate and branched chain amino acids (BCAA) • Growth and development assessed as Z scores for height (or length), weight, BMI and BSA and change in these parameters over time • Rate of use of nasogastric or G tube for administration of UCD medication • Change in weekly mean and maximal ammonia levels for subjects with ammonia values higher than upper limit of normal during the Pre-Enrolment period versus those on HPN-100 • palatability	Started	December 2018
Non-interventional, observational multi-center registry to be conducted in patients with urea cycle	To address safety concerns of growth and neurocognitive outcomes and to	Outcome variables and assessments • control of blood ammonia	Started	Registry. See Annex 6 for proposed protocol

disorders (UCDs) (HPN-100-014). Category: 3	generate comparative effectiveness data in UCD patients.	levels and frequency of hyperammonaemic crises • frequency of SAEs • neuropsychological test scores • growth and development assessments • UCD medication discontinuation or change in medication		synopsis
A Randomized, Controlled, Open-Label Cross Over Study of the Safety, Pharmacokinetics and Ammonia Control of RAVICTI® (Glycerol Phenylbutyrate [GPB]) Oral Liquid and Sodium Phenylbutyrate (NaPBA) in Phenylbutyrate Treatment Naïve Patients with Urea Cycle Disorders (UCDs). (Study Number HPN-100-021) Category: 3	To assess the safety, pharmacokinetics, and ammonia control of RAVICTI and Sodium Phenylbutyrate (NaPBA) in UCD subjects not currently treated with phenylacetic acid prodrugs.	**Cross over Endpoints:** *Primary:* Blood ammonia *Secondary:* Assessment of adverse events Drug preference *Exploratory* Rate of drug discontinuation due to adverse events UCD symptoms **Safety Extension Endpoints** *Primary:* Blood ammonia including hyperammonaemic crisis (HAC) *Secondary:* Changes in CGI scales (Investigator and Patient) Assessment of adverse events *Exploratory* Rate of drug discontinuation due to adverse events	Planned	March 2017
European Post-Marketing RAVICTI Registry in Partnership with E-IMD Category: 1	Apart from the data already collected in the E-IMD the registry will additionally gather information on long term safety, the incidence rate and type of cancer in the patient population, PAA toxicity, the use in patients with renal impairment as well as the use during pregnancy and lactation in patients treated with RAVICTI. This registry will further elucidate the safety and efficacy of RAVICTI in patients with characteristics not previously	• Long term safety • Carcinogenicity • PAA toxicity • Exposure during pregnancy lactation • Renal impairment	Planned	Will be provided with the due PSURs Final planned report July 2030

	studied in the clinical development programme. The registry will also include paediatric patients. It is planned to include about 100 patients in this registry.			

[a]Protocol HPN-100-009 is designed to address the PDCO PIP Agreement. EMA-000297-PIP02-12M01))

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Gastrointestinal Effects	**SmPC, Section 4.8** Common gastrointestinal adverse drug reactions. Flatulence, diarrhoea, vomiting, nausea, abdominal pain upper, abdominal pain, dyspepsia, abdominal distension, constipation, oral discomfort, retching, Uncommon gastrointestinal adverse drug reactions. Abdominal discomfort, abnormal faeces, dry mouth, eructation, defaecation urgency, upper abdominal pain and/or lower abdominal pain, painful defaecation, steatorrhoea, stomatitis	None
Toxicity due to the active metabolite PAA (Phenylacetic acid)	**SmPC, Section 4.2** *Adjustment Based on Plasma Phenylacetate and Phenylacetylglutamine* Symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness in the absence of high ammonia or intercurrent illness may be signs of phenylacetic acid (PAA) toxicity (see section 4.4, PAA toxicity). Therefore, measurement of plasma PAA and PAGN levels may be useful to guide dosing. The plasma PAA to PAGN (both measured in mcg/ml) ratio has been observed to be generally less than 1 in patients without PAA accumulation. In patients with a PAA to PAGN ratio exceeding 2.5, 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. In such cases, increasing the dosing frequency may result in a lower plasma PAA level and PAA to PAGN ratio. Ammonia levels must be monitored closely when changing the dose of RAVICTI. *Adjustment based on urinary phenylacetylglutamine* U-PAGN measurements may be used to help guide RAVICTI dose adjustment and assess compliance. 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 recommended ULN, the RAVICTI dose should be adjusted upward. The amount of dose adjustment	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	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. Spot U-PAGN concentrations below the following levels may indicate improper medicinal product administration and/or lack of compliance: • 9000 microgram (mcg/ml) for patients under 2 years of age • 7000 microgram (mcg/ml) for patients ≥2 years of age with a BSA of ≤1.3 • 5000 microgram (mcg/ml) for patients ≥2 years of age with a BSA of >1.3 If spot U-PAGN concentrations fall below these levels, assess compliance with medicinal product and/or effectiveness of medicinal product administration (e.g., via feeding tube) and consider increasing the RAVICTI dose in compliant patients to achieve optimal ammonia control (within normal limit for patients under 2 years of age and less than half ULN in older patients when fasted). **SmPC, Section 4.4** *PAA Toxicity* Reversible clinical manifestations suggestive of neurotoxicity (e.g., nausea, vomiting, somnolence) have been reportedly associated with phenylacetate levels ranging from 499-1285 mcg/ml in cancer patients who received PAA intravenously. Although these have not been seen in clinical trials involving UCD patients, high PAA levels should be suspected in patients with unexplained somnolence, confusion, nausea and lethargy who have normal or low ammonia. If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other intercurrent illnesses, measure plasma PAA and plasma PAA to PAGN and consider reduction of RAVICTI dosage or increase the frequency of dosing if the PAA level exceeds 500 mcg/L and the plasma PAA to PAGN ratio exceeds 2.5. **SmPC, Section 4.9** PAA, the active metabolite of glycerol phenylbutyrate, is associated with signs and symptoms of neurotoxicity (see section 4.4) and could accumulate in patients who receive an overdose. In case of overdose, discontinue the drug and monitor the patient for any signs or symptoms of adverse reactions.	
	RAVICTI will be subject to **restricted** medical prescription.	
Drug-Drug Interactions (Affecting GPB)	**SmPC, Section 4.5** A medicinal product interaction study was performed with glycerol phenylbutyrate. Exercise caution in the	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	concomitant use of medicinal products known to inhibit lipase given that glycerol phenylbutyrate is hydrolysed by digestive lipase into phenylbutyrate acid and glycerol. This may be associated with increased risk of medicinal product interactions with lipase inhibitors and with lipase contained in pancreatic enzyme replacement therapies. A potential effect on CYP2D6 isoenzyme cannot be excluded and caution is advised for patients who receive medicinal products that are CYP2D6 substrates. Glycerol phenylbutyrate and/or its metabolites, PAA and PBA, have been shown to be weak inducers of CYP3A4 enzyme *in vivo*. *In vivo* exposure to glycerol phenylbutyrate has resulted in decreased systemic exposure to midazolam of approximately 32% and increased exposure to the 1-hydroxy metabolite of midazolam, suggesting that steady-state dosing of glycerol phenylbutyrate results in CYP3A4 induction. The potential for interaction of glycerol phenylbutyrate as a CYP3A4 inducer and those products predominantly metabolised by the CYP3A4 pathway is possible. Therefore, therapeutic effects and/or metabolite levels of medicinal products, including some oral contraceptives that are substrates for this enzyme may be reduced and their full effects cannot be guaranteed, following co-administration with glycerol phenylbutyrate. Effects of glycerol phenylbutyrate on other CYP isoenzymes have not been studied in humans and cannot be excluded. RAVICTI will be subject to **restricted** medical prescription.	
Drug-Drug Interactions (Affecting Ammonia)	**SmPC, Section 4.4** *Potential for other medicinal products to affect ammonia* *Corticosteroids* Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Monitor ammonia levels closely when corticosteroids and glycerol phenylbutyrate are used concomitantly. *Valproic Acid and Haloperidol* Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in UCD patients. *Probenecid* Probenecid may inhibit the renal excretion of metabolites of glycerol phenylbutyrate including PAGN. RAVICTI will be subject to **restricted** medical prescription.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in patients with hepatic impairment	**SmPC, Section 4.2** *Hepatic impairment* Because conversion of PAA to PAGN occurs in the liver, patients with severe hepatic impairment may have reduced conversion capability and higher plasma PAA and plasma PAA to PAGN ratio. Therefore, dosage for adult and paediatric patients with mild, moderate or severe hepatic impairment should be started at the lower end of the recommended dosing range (4.5 ml/m^2/day) and kept at the lowest dose necessary to control the patient's ammonia levels. A plasma PAA to PAGN ratio exceeding 2.5 may indicate saturation of PAA to PAGN conversion capacity and the need for reduced dosing and/or increased frequency of dosing. The plasma PAA to PAGN ratio may be useful in dosage monitoring. (see section 5.2). **SmPC, Section 5.2** Hepatic impairment In a study in patients with clinically decompensated cirrhosis and hepatic encephalopathy (Child-Pugh B and C), mean C_{max} of PAA was 144 microgram/ml (range: 14-358 microgram /ml) after daily dosing of 6 ml of glycerol phenylbutyrate twice daily, while mean C_{max} of PAA was 292 micrograms /ml (range: 57-655 microgram/ml) after daily dosing of 9 ml of glycerol phenylbutyrate twice daily. The ratio of mean values for PAA to PAGN among all patients dosed with 6 ml BID ranged from 0.96 to 1.28 and for patients dosed with 9ml twice daily ranged from 1.18-3.19.After multiple doses, a PAA concentration >200 microgram /L was associated with a ratio of plasma PAA to PAGN concentrations higher than 2.5. These findings collectively indicate that conversion of PAA to PAGN may be impaired in patients with severe hepatic impairment and that a plasma PAA to PAGN ratio > 2.5 identifies patients at risk of elevated PAA levels.	None
	RAVICTI will be subject to **restricted** medical prescription.	
Use in patients with renal impairment	**SmPC, Section 4.2** *Renal impairment* No studies were conducted in UCD patients with renal impairment; the safety of RAVICTI in patients with renal impairment is unknown. RAVICTI should be used with caution in patients with severe renal impairment. Preferably such patients should be started and maintained at the lowest dose necessary to control the blood ammonia levels. **SmPC, Section 4.4** *Potential for other drugs to affect glycerol phenylbutyrate* *Probenecid* Probenecid may inhibit the renal excretion of metabolites of glycerol phenylbutyrate including PAGN. **SmPC, Section 5.2**	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Renal impairment The pharmacokinetics of glycerol phenylbutyrate in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on haemodialysis have not been studied. RAVICTI will be subject to **restricted** medical prescription.	
Exposure during pregnancy	**SmPC, Section 4.4** *Pregnancy* RAVICTI should not be used during pregnancy and in women of childbearing potential not using contraception unless the clinical condition of the woman requires treatment with glycerol phenylbutyrate, see section 4.6. **SmPC, Section 4.6** Pregnancy Studies in animals have shown reproductive toxicity (see section 5.3).There are limited data regarding the use of glycerol phenylbutyrate in pregnant women.Glycerol phenylbutyrate is not recommended during pregnancy and in women of childbearing potential not using contraception. RAVICTI will be subject to **restricted** medical prescription.	None
Exposure during lactation	**SmPC, Section 4.6** Breast-feeding It is unknown whether glycerol phenylbutyrate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from glycerol phenylbutyrate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. RAVICTI will be subject to **restricted** medical prescription.	None
Overdose	**SmPC, Section 4.9** PAA, the active metabolite of glycerol phenylbutyrate, is associated with signs and symptoms of neurotoxicity (see section 4.4) and could accumulate in patients who receive an overdose. In case of overdose, discontinue the drug and monitor the patient for any signs or symptoms of adverse reactions. RAVICTI will be subject to **restricted** medical prescription.	None
Carcinogenicity	**SmPC, Section 5.3** *Carcinogenesis* In a rat study, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma in males and females, at a dose of 4.7 and 8.4 times the dose in adult patients, (6.87 ml/m^2/day based on combined AUCs for PBA and PAA). The incidence of the following tumours was also increased in female rats: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	cortical combined adenoma or carcinoma, cervical schwannoma, uterine endometrial stromal polyp, and combined polyp or sarcoma. Glycerol phenylbutyrate was not tumourigenic at doses up to 1000 mg/kg/day in a 26-week mouse study. Glycerol phenylbutyrate has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and shown no genotoxic activity. RAVICTI will be subject to **restricted** medical prescription.	
Impaired Fertility	**SmPC, Section 4.6** Fertility Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats (see section 5.3). There are no data for human fertility. **SmPC, Section 5.3** *Impairment of Fertility* Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at clinical exposure levels, however at oral doses up to approximately 7 times the dose in adult patients, maternal as well as male toxicity was observed and the number of nonviable embryos was increased. RAVICTI will be subject to **restricted** medical prescription.	None
Off-label use	**SmPC, Section 4.1** Therapeutic indications RAVICTI is indicated for use as a nitrogen-binding medicinal product for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs – including deficiencies of carbamoyl phosphate synthetase I (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS, also called citrullinemia I), arininosuccinate lyase (ASL, also called arginosuccinic aciduria), arginase I (ARG) and ornithine translocase (also called HHH [Hyperammonaemia-Hyperornithinemia-Homocitrullinemia Syndrome]) 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). RAVICTI will be subject to **restricted** medical prescription.	None
Reduced phenylbutyrate absorption in pancreatic insufficiency or intestinal malabsorption	**SmPC, Section 4.4** *Reduced phenylbutyrate absorption in pancreatic insufficiency or intestinal malabsorption* Exocrine pancreatic enzymes hydrolyse RAVICTI in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	absent digestion of RAVICTI and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Ammonia levels should be closely monitored in patients with pancreatic insufficiency or intestinal malabsorption. RAVICTI will be subject to **restricted** medical prescription.	
Use in pre-term newborns and neonates	**SmPC, Section 4.2** *Paediatric population* *Patients from birth to < 2 Months of Age* The safety and efficacy of RAVICTI in children <2 months of age have not yet been established. No data are available. RAVICTI will be subject to **restricted** medical prescription.	None
Use in the elderly ≥ 65 years	**SmPC, Section 4.2** *Elderly (65 years or older)* Clinical studies of RAVICTI did not include sufficient numbers of subjects ≥ 65 years of age to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other medicinal product therapy. RAVICTI will be subject to **restricted** medical prescription.	None
Use in UCD subtype NAGS deficiency	**SmPC, Section 4.2** **N-acetylglutamate synthase (NAGS) deficiency** The safety and efficacy of RAVICTI for the treatment of patients with N-acetylglutamate synthase (NAGS) deficiency has not been established. RAVICTI will be subject to **restricted** medical prescription.	None
Long term safety	No specific information required beyond the general instructions. RAVICTI will be subject to **restricted** medical prescription.	None
Use in UCD subtype CITRIN deficiency	**SmPC, Section 4.2** **CITRIN (citrullinaemia type 2) deficiency** The safety and efficacy of RAVICTI for the treatment of patients with CITRIN (citrullinaemia type 2) deficiency has not been established. **RAVICTI will be subject to restricted medical prescription.**	None

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ravicti (glycerol phenylbutyrate) 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.

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

Benefits

Beneficial effects

Urea Cycle Disorders are very rare, serious and life threatening disorders comprising a group of inherited deficiencies of one of the enzymes or transporters involved in the urea cycle, which converts ammonia to urea. Absence or severe dysfunction of the enzymes or transporters results in accumulation of toxic levels of ammonia in the blood and brain of affected patients. Although genetically distinct, the Urea Cycle Disorders share important features and are therefore typically considered as a group. The most important clinical manifestations common to Urea Cycle Disorders are attributable to hyperammonaemia.

Although the less severe Urea Cycle Disorders subtypes can be managed by dietary protein restriction and/or amino acid supplementation alone, for most of them, this therapy is less than satisfactory, thus an unmet medical need has therefore to be considered. NaPBA is the only currently approved treatment in EU for the treatment UCDs since 1999 (AMMONAPS) and more recently as PHEBURANE.

RAVICTI (HPN-100) consists of three molecules of phenylbutyric acid (PBA) joined to glycerol to form a short-chain triglyceride, which appears to be digested by pancreatic lipases to release PBA. Regarding the pharmacodynamics activity of the compound, RAVICTI (HPN-100) has the same mechanism of action as sodium phenylbutyrate (NaPBA).

The applicant provided results from one pivotal randomised study in adults patients (study HPN -100-006) with Urea Cycle Disorders and five supportive studies in the paediatric population in children above 2 months of age. Short term results and long term are provided in the application. The studies investigated the use in patients with Urea Cycle Disorders in the following subgroups of patients older than 2 months and suffering from UCD: including deficiencies of carbamoyl phosphate-synthase-I, ornithine carbamoyltransferase, argininosuccinate synthetase, argininosuccinate lyase, arginase I,

ornithine translocase deficiency and hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome.
RAVICTI is intended for the treatment of urea cycle disorders in adults and on children over 2 months. There are no data provided for children less than two months.

The results of the primary analysis of the pivotal study (HPN 100-006) including 51 adult patients provide evidence of non-inferiority of HPN-100 to NaPBA in terms of levels of blood ammonia. Consistent results were seen for analyses of the mITT and per protocol populations. Overall, there were no significant differences between treatment groups either patients who received RAVICTI and those who received the active comparator NaPBA. However, it is acknowledged that the sustained release characteristics provided a better control during the day allowing nitrogen waste removal to occur more evenly.

Overall, the use of both RAVICTI and NaPBA offer a benefit across the majority of the efficacy outcome measures. In particular, efficacy was demonstrated in the reduction for both blood ammonia and glutamine.

The analysis of fasting ammonia in relation to both short term ammonia exposure and hyperammonaemic crises indicate that the fewer crises observed on HPN-100 is a result of the better ammonia control. In the long term studies, the clinical relevance of the ammonia control is reflected in improved long-term outcomes, including approximately 50% fewer total hyperammonaemic crises during 12 months of dosing with HPN-100 as compared with the prior 12 months during dosing with NaPBA.

In short term studies performed in the paediatric population (49 patients from 2 months of age), a statistical difference in favour of HPN-100 versus NaPBA in controlling blood ammonia levels, as measured by AUC_{0-24} (774.11 versus 991.19 µmol·h/L, respectively), was shown in the pooled analysis of 80 patients aged 2 months through over 70 years who underwent 24-hour ammonia monitoring during equivalent, steady state dosing of both drugs.

Across the studies, the mean urinary PAGN 0- 24 excretion (secondary endpoint) was similar between the two HPN-100 and NaPBA treatment groups.

There were no apparent differences in response to the study medication between the different subgroups of UCDs. More importantly, the numbers of the subgroups are quite small for any meaningful interpretation of the results per subgroup.

RAVICTI offers advantages over NaPBa in terms of absence of sodium, removal of pill burden as it administered in the form of a solution, and may therefore be more palatable particularly to children.

Additionally, for patients who have compromised neurological functioning due to their inherent UCD, Ravicti is an improved formulation with flexibility to be easily administered either via nasogastric tube or gastrostomy tube compared with the current approved product formulations.

The use of RAVICTI is however limited to the chronic management of UCDs in specific subtypes and not for the treatment of patients with acute hyperammonaemia as more rapidly acting interventions are essential to reduce plasma ammonia levels.

Ravicti must be used with dietary protein restriction and sometimes dietary supplements based on the UCD subtype. A total daily range dose is recommended between 4.5 ml/m^2/day and 11,2 mL/m^2/day. The daily dose should be individually adjusted according to the patient's protein tolerance and the daily dietary protein intake needed.

Uncertainty in the knowledge about the beneficial effects.

The long term data provided are based on uncontrolled studies. The lack of controlled long term study data is obviously unsatisfactory and contributes significantly to the uncertainty regarding the knowledge about the beneficial effects. Although it is recognised that the urea cycle disorders are rare diseases, with patient recruitment difficulties, these are nevertheless chronic conditions which require to be studied over long term treatment.

The database for long term continuous treatment in open label studies shows that RAVICTI may be effective when administered chronically. However, in the absence of controlled study data, this is difficult to draw definite conclusions. Therefore there is a need to gather further long term efficacy data in the post marketing setting. A disease registry has been agreed as part of the Marketing authorisation in order to follow patients and provide results regular results on efficacy and safety data.

Additionally only 6 subtypes of Urea cycle disorders have been studied. Therefore the indication is limited in these subtypes including deficiencies of carbamoyl phosphate-synthase-I, ornithine carbamoyltransferase, argininosuccinate synthetase, argininosuccinate lyase, arginase I and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome .

Risks

Unfavourable effects

The clinical safety database of UCD patients treated with HPN-100 over short and long term safety extension studies is adequate in both adults and paediatric populations above 2 years and includes representation of 6 out of the 7 subtypes. The adverse events reported by patients during short term treatment with RAVICTI were generally similar both in frequency and type to those reported by patients receiving the active comparator, NaPBA.

The most frequently reported adverse reactions were diarrhoea, flatulence, headache (8.8%), decreased appetite (7%), vomiting (6.1%), fatigue, nausea and abnormal skin odour (5.3%).

The incidences of adverse events were similar across the population subgroups including gender' race or UCD subtype and there was no trend toward an increase in the incidence of any TEAE with long-term exposure with study medications.

Seemingly, a larger proportion of patients developed serious adverse events in open label studies even when taking into account the longer duration of exposure the study medication. Although due to lack of controlled data in long-term studies, no definite conclusions can be drawn on the occurrence of these serious adverse events in the long term studies.

The safety data show that HPN-100 have minimal effects on the hepatic function. In patients with hepatic impairment, reduced conversion capability is expected resulting in higher plasma phenylacetic acid (PAA) and plasma PAA to phenylacetylglutamine ratio. Therefore, dosage for patients with mild, moderate to severe hepatic would need to be reduced. It is recommended to start at the lower range of the recommended dose.

In the paediatric short-term controlled studies, a smaller proportion of paediatric than adult patients reported a TEAE with HPN-100 and NaPBA treatments. The safety profile appears similar than in adults with however few ADRs not observed in adults. However, due to the limited exposure no definite conclusion can be drawn.

Uncertainty in the knowledge about the unfavourable effects

There is limited formal pharmacokinetic study data which tend to suggest that the pharmacokinetics of RAVICTI may not have been fully characterised. However, the data available and the knowledge about the currently authorised product containing NaPBa, provide further scientific data taking into account the similarity of RAVICTI and NaPBa in term of mechanism of action.

Apart from the one study no other interaction studies have been performed. However, the potential for adverse interaction with some other preparations commonly used in these disease conditions may exist.

The safety profile over long term remains not fully characterised in the subtypes studied. Therefore the company is requested to provide long term data for a period of 10 years through a disease registry.

Benefit-risk balance

Importance of favourable and unfavourable effects

The results of the primary analysis of the pivotal study provide evidence of non-inferiority of HPN-100 to NaPBA in terms of levels of blood ammonia. Consistent results were seen for analyses of the mITT and per protocol populations. Ravicti has been shown to exert beneficial effects in a consistent manner in form of reduction for both blood ammonia and glutamine on adult and paediatric patients. Overall, the results of short term studies provide clinically relevant results in some subtypes of UCD.

The observed favourable effects are considered to be clinically relevant in the adult and paediatric population above 2 months of age.

The unfavourable effects appear to be restricted to relatively minor complaints of body odour, abdominal pain and nausea for patients of all age groups. In paediatric patients, vomiting, body odour and abdominal pain/distress were most common. However, there is some uncertainty regarding the adverse events profile especially in the long term as no definite conclusions can be drawn on the incidence of the serious adverse events in open label studies.

The safety and efficacy of RAVICTI for the treatment of patient less than 2 months of age and/or patients with N-acetylglutamate synthase (NAGS) deficiency has not been established.

Benefit-risk balance

Discussion on the benefit-risk balance

The observed favourable effects are considered to be clinically relevant in the adult and paediatric population above 2 months of age and sufficiently demonstrated in sub group of patients with Urea cycle disorders (eg in patients with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH syndrome).

There are however no data in paediatric patients below 2 months of age. Further studies will be provided in the post approval setting.

The sustained release characteristics of RAVICTI allow waste nitrogen removal, which occurs evenly throughout the day. This effect results in better blood ammonia control throughout the day with reduction in hyperammonaemic events observed in UCD patients.

Finally, there is limited information in relation to chronic use on patients with UCDs. The disease registry requested by CHMP will provide further information in the post authorisation setting.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ravicti as follows:
"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)."

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): Multi-centre prospective non-interventional registry in patients with urea cycle disorders on treatment with glycerol phenylbutyrate to characterise patients` demographics, and to document long-term safety and clinical outcomes	Final study report expected in July 2030.

New Active Substance Status

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that the active substance glycerol phenylbutyrate is to be considered a new active substance in comparison to the known substance, sodium phenylbutyrate previously authorised in the European Union, as it differs significantly in properties with regard to safety and efficacy from the previously authorised substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0068/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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