Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sodium phenylbutyrate

Proprietary Product Name: Pheburane

Sponsor: Orpharma Pty Ltd

January 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
°C	Degree Celsius
AE	Adverse Event
ANCOVA	Analysis Of Covariance
ANOVA	Analysis Of Variance
ARRB	Allergic Reaction Review Board
ASL	Argininosuccinate Lyase
ASS	Argininosuccinate Synthetase
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BCAA	Branched chain amino acid
CL	Total clearance of drug after intravenous administration
C_{max}	Observed maximum plasma concentration
CNS	Central Nervous System
CP	Carbamyl Phosphate
CPS-I	Carbamyl Phosphate Synthetase I
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPB	Glycerol Phenylbutyrate

Abbreviation	Meaning
HAQ	Health Assessment Questionnaire
IAR	Infusion associated reaction
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
NAGS	N-acetylglutamate synthase
NaPB	Sodium phenylbutyrate
NH3	Ammonia
OTC	Ornithine transcarbamylase deficiency
PAA	Phenylacetic Acid
PAGN	Phenylacetylglutamine
PBA	Phenylbutyric Acid
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
qow	Every other week
REB	Research Ethics Board
RFTs	Respiratory Function Tests
SAE	Serious Adverse Event

Abbreviation	Meaning
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$T_{½}$ or $t_{½}$	Elimination half-life
T_{max}	Time to reach C_{max}
UCD	Urea Cycle Disorders
Vd	Apparent volume of distribution
Vdz	Apparent volume of distribution based upon the terminal phase
Vdz	Apparent volume of distribution based upon the terminal phase
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	19 May 2017
Date of entry onto ARTG	30 May 2017
Active ingredient(s):	Sodium phenylbutyrate
Product name(s):	Pheburane
Sponsor's name and address:	Orpharma Pty Ltd Level 1, 1 Queens Road Melbourne, Victoria 3004
Dose form(s):	Granules
Strength(s):	483 mg/g
Container(s):	High-density polyethylene (HDPE) bottle, with a polypropylene (PP) Child Resistant Cap (CRP), desiccant and calibrated measuring spoon
Pack size(s):	174 g granules (equivalent to 84 g sodium phenylbutyrate)
Approved therapeutic use:	*Pheburane (sodium phenylbutyrate) is indicated for the management of hyperammonaemia associated with urea cycle disorders. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, and protein-free calorie supplements)*
Route(s) of administration:	Oral (PO)
Dosage:	The usual total daily dose of sodium phenylbutyrate is: · up to 600 mg/kg/day in neonates, infants and children weighing less than 20 kg; · up to 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults. The safety and efficacy of doses in excess of 20 g/day have not been established. The recommended dose is expressed in terms of milligrams (mg) or grams (g) of sodium phenylbutyrate, rather than the weight of the granules. A calibrated dosing spoon is provided which dispenses Pheburane granules equivalent to amounts up to 3 g of sodium phenylbutyrate in graduations of 250 mg. Use ONLY the dosing spoon provided with the medicine to measure out the dose. DO NOT use any other measuring device to measure out the dose.
ARTG number (s):	273750

Product background

This AusPAR describes the application by the sponsor Orpharma Pty Ltd to register a new chemical entity, sodium phenylbutyrate as Pheburane for the treatment of patients with urea cycle disorders as follows:

> *Pheburane (sodium phenylbutyrate) is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements).*
>
> *Pheburane is indicated in patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.*
>
> ***Geriatrics (> 65 years of age)***
>
> *Pheburane has not been studied in the geriatric population.*

Pheburane is proposed to be used as adjunctive therapy in the management of urea cycle disorders (UCDs), including those with either neonatal or later onset (associated with a history of hyperammonaemic encephalopathy).

Pheburane granules are to be given orally (PO) as a lifetime treatment in combination with dietary protein restriction, and with dietary supplementation as required.

The dose rate, based on plasma monitoring, is

- 450 to 600 mg/kg/day in neonates, infants and children weighing less than 20 kg, and
- 9.9 to 13.0 mg/m^2 in children weighing over 20 kg, adolescents and adults, up to a maximum of 20 g/day (Tables 1-2).

It may also be administered by nasogastric or gastrostomy tube as a 50 mg/mL solution. (Tables 3-4)

Table 1: Recommended doses of Pheburane granules for oral dosing in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval of sodium phenylbutyrate		Dosing interval of Pheburane granules	
	Minimum dose (mg) per day	Maximum dose (mg) per day	Minimum dose (mg) per day	Maximum dose (mg) per day
3	1350	1800	2795	3700
4	1800	2400	3700	4900
5	2250	3000	4600	6200
7.5	3375	4500	7000	9300
10	4500	6000	9300	12400
15	6750	9000	14000	18600

Weight (kg)	Dosing interval of sodium phenylbutyrate		Dosing interval of Pheburane granules	
20	9000	12000	18600	24850

Table 2: Recommended doses of Pheburane granules for oral dosing in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval of sodium phenylbutyrate		Dosing interval of Pheburane granules	
	Minimum dose (g) per day	Minimum dose (g) per day	Minimum dose (g) per day	Maximum dose (g) per day
0.8	7.9	10.4	16.4	21.5
1.05	10.4	13.7	21.5	28.4
1.27	12.6	16.5	26.1	34.2
1.48	14.7	19.2	30.4	39.8
1.66	16.4	20.0*	34	41.4
1.84	18.2	20.0*	37.7	41.4
1.97	19.5	20.0*	40.4	41.4

The safety and efficacy of doses in excess of 20 g/day have not been established.

Recommended doses for administration of Pheburane solution through nasogastric or gastrostomy tube are shown in Table 3 and Table 4.

Table 3: Recommended doses of Pheburane solution (50 mg/mL of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
3	27.0	36.0
4	36.0	48.0
5	45.0	60.0
7.5	67.5	90.0
10	90.0	120.0
15	135.0	180.0

Weight (kg)	Dosing interval	
20	180.0	240.0

Table 4: Recommended doses of Pheburane solution (50 mg/ml of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
0.8	158.4	208.0
1.05	207.9	273.0
1.27	251.5	330.2
1.48	293.0	384.8
1.66	328.7	400.0*
1.84	364.3	400.0*
1.97	390.1	400.0*

*The safety and efficacy of doses in excess of 20 g/day have not been established.

The urea cycle is the metabolic pathway that incorporates waste nitrogen into urea for excretion. Excess dietary protein and the nitrogenous substances produced by endogenous protein turnover are normally metabolised to yield energy and the by-product ammonia is transformed into nontoxic urea which is freely excreted in the urine. The urea cycle also synthesises and degrades arginine.

Urea Cycle Disorders (UCD) are inherited deficiencies of one of the 6 enzymes involved:

- N-Acetyl glutamate synthetase (NAGS)
- Carbamyl phosphate synthetase (CPS-I)
- Ornithine transcarbamylase (OTC)
- Argininosuccinate synthetase (ASS)
- Argininosuccinate lyase (ASL)
- Arginase Deficiency (ARG1).

The urea cycle disorders (UCDs) are a group of inborn errors of metabolism in one of the 6 enzymes listed above. These disorders may be diagnosed in early childhood or with milder deficiencies in adulthood. Conditions that lead to increased demands on the urea cycle such as protein load, infection, systemic corticosteroids, rapid weight loss, surgery, trauma and chemotherapy can precipitate decompensation.

Deficiencies of CPS1, ASS1, ASL, NAGS and ARG have autosomal recessive inheritance and OTC deficiency has X-linked inheritance.

Figure 1: The Urea Cycle

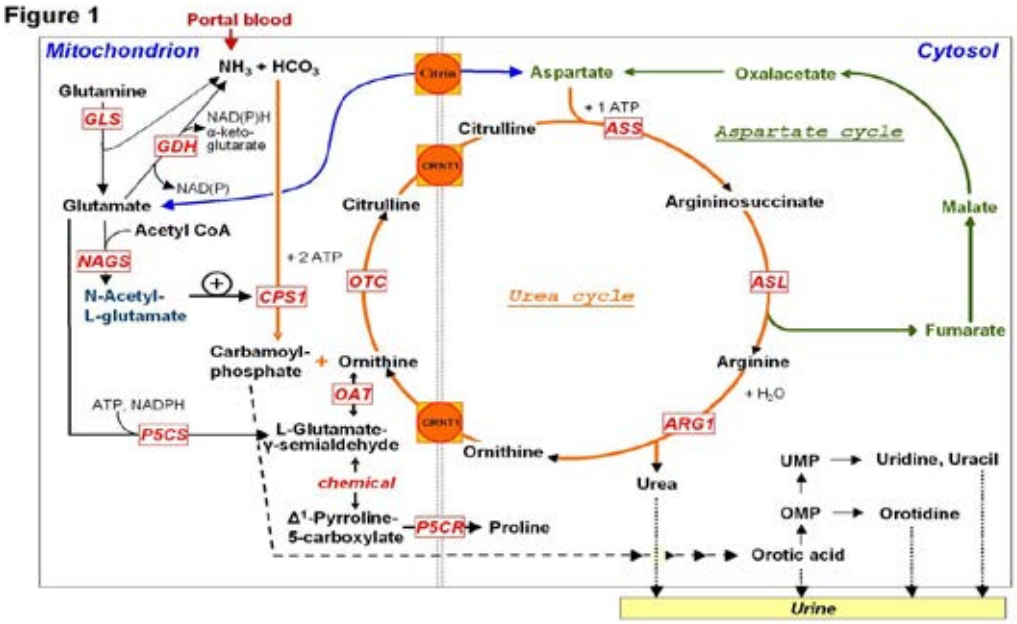
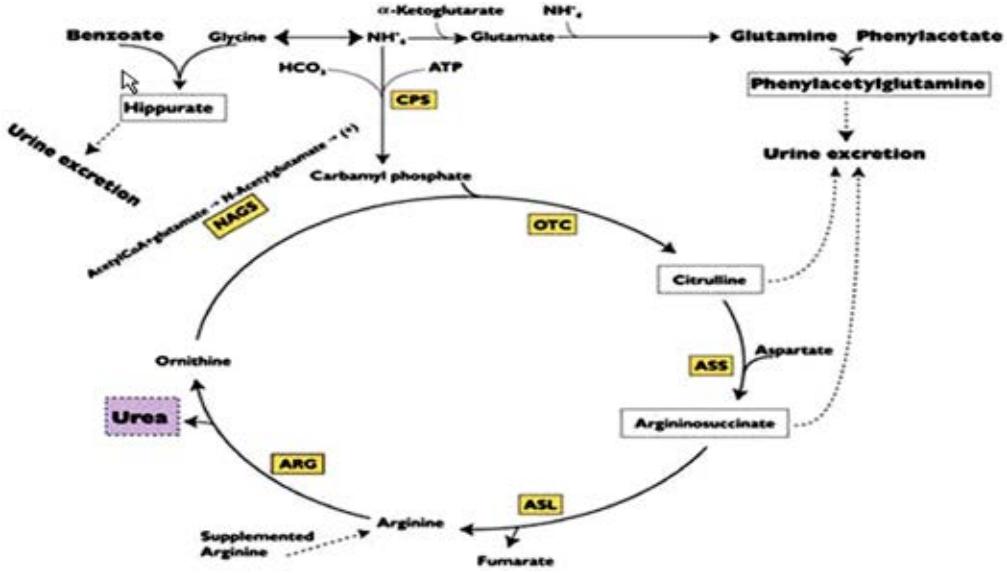


Figure 2: Waste nitrogen removal using sodium phenylbutyrate



The initial presentation varies widely from severe acute hyperammonaemia causing a rapidly progressive, often fatal encephalopathy with cerebral oedema, impaired conscious state, often seizures, followed by respiratory arrest and death or permanent brain injury through to neuropsychiatric illness from chronic milder hyperammonaemia in infancy and milder forms of the disease manifesting in childhood or in adults with a dietary avoidance of protein. Encephalopathy may be misdiagnosed for years or severe symptoms may not occur until triggered during times of stress or illness.

Three main components of therapy for UCDs comprise a low protein diet that balances the nutritional and growth requirements with nitrogen waste, nutritional supplementation with citrulline or arginine and pharmacological intervention with nitrogen scavenger therapy of which sodium phenylbutyrate is one. Event with treatment metabolic decompensation can recur episodically triggered by endogenous protein loads or exogenous protein catabolism. The cure for UCDs is liver transplantation.

Sodium phenylbutyrate (sodium phenylbutyrate, sodium - 4 phenylbutanoate) is an ammonium scavenger. It is a pro-drug, rapidly metabolised to phenylacetate (PAA). PAA conjugates with glutamine by acetylation to form phenylacetylglutamine (PAGN) which is then excreted in the kidneys. Each mole of PAGN can bind 2 moles of nitrogen, comparable to urea, and therefore provides an alternate means of nitrogen waste excretion.

Sodium phenylbutyrate was developed because PAA has, and causes patients to have, an offensive odour. Sodium phenylbutyrate has a very bitter taste that is not easily disguised and compliance with therapy can be compromised due to poor tolerability. Strategies including administration by nasogastric tube and extemporaneous compounding have been described to overcome this problem for adults and children (for dosing see Tables 3-4). Pheburane was developed as a coated granule to reduce/remove the bitter taste associated with the phenylbutyrate (PBA).

The submission was a mixed (hybrid) submission using published literature and a bioequivalence trial, presented in the NeeS electronic format to support their application.

Relevant TGA adopted European Union (EU) guidelines, in addition to the general guidelines, are:

- CPMP/EWP/QWP/1401/98 Rev.1/Corr Guideline on the Investigation of Bioequivalence
- EMEA/CHMP/EWP/147013/2004 Corr Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population
- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use

The TGA guidance on literature based submissions published on the TGA website (https://www.tga.gov.au/publication/literature-based-submissions) is also of relevance for this submission.

Regulatory status

The product is a new chemical entity for Australian registration purposes. It was first entered on the Australian Register of Therapeutic Goods (ARTG) on the 30 May 2017.

Pheburane was granted orphan status on 13 August 2014 for the *Treatment of urea cycle disorders.* Sodium phenylbutyrate has not previously been considered by the TGA's advisory committees.

The product has been approved in Canada, European Union (EU), New Zealand, Israel, South Korea and Columbia (see Table 5 below).

Table 5: International regulatory status

Name of the country	Product name and strength	Status	Date of Approval
Canada	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	Jan 26, 2015
European Union	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	July 31, 2013
New Zealand	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	Oct 29, 2015
Israel	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	Mar 16, 2015
South Korea	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	Aug 21, 2015
Columbia	PHEBURANE 483mg/g sodium phenylbutyrate	Approved	July 29, 2016

Similar products approved overseas include Ammonaps in the EU (sodium phenylbutyrate 500 mg tablets, originally approved in 1999), Buphenyl (sodium phenyl butyrate tablets and powder, approved in 1996) and Ravicti (glycerol phenylbutyrate oral liquid, 1.1 g/mL, approved in 2013 in the US and 2015 in the EU).

Sodium phenylbutyrate has been used since 1987 in the US under an IND (the Investigational New Drug programme in the US). Formulations of sodium phenylbutyrate are registered in the US (1996) and in the EU (1999).

In the EU Ammonaps as 940 mg/g sodium phenylbutyrate granules and Pheburane as 483 mg/g sodium phenylbutyrate granules are approved for:

> *indicated as adjunctive therapy in the chronic management of urea cycle disorders involving deficiencies of carbamylphosphatee synthetase, ornithine transcarbamylase or argininosuccinate synthetase.*
>
> *It is indicated in all patients with neonatal presentations (complete enzyme deficiencies presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (patrial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.*

In New Zealand and Canada Pheburane has a similar indication:

> *Pheburane (sodium phenylbutyrate) indicated as adjunctive therapy in the chronic management of urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.*
>
> *It is indicated in all patients with neonatal presentations (complete enzyme deficiencies presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (patrial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.*
>
> ***Geriatrics (>65 years of age)***
>
> *Pheburane has not been studied in the geriatric population.*

In the US Buphenyl (glycerol phenylbutyrate (GPB)) is available as powder or 500 mg tablets and has the indication:

> *Buphenyl is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamoyl synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). It is indicated in patients with late-onset disease (partial enzymatic deficiency presenting after the first month of life) who have a history of hyperammonemic encephalopathy.*

It is important that the diagnosis be made early and treatment initiated immediately to improve survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency.

Buphenyl must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation (See Nutritional Supplementation subsection of Dosage and Administration)

The registered product (sodium phenylbutyrate 483mg/g granules) in the European Union, New Zealand and Canada has the same formula, dosage form, manufacturing process as the product proposed for Australia.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II Registration timeline

Table 6: Registration timeline for Submission PM-2016-00417-1-3

Description	Date
Submission dossier accepted and 1st round evaluation commenced	2 May 2016
1st round evaluation completed	30 September 2016
Sponsor provides responses on questions raised in 1st round evaluation	24 November 2016
2nd round evaluation completed	24 January 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	6 March 2017
Sponsor's pre-Advisory Committee meeting response	20 March 2017
Advisory Committee meeting	6-7 April 2017
Registration decision	19 May 2017
Entry onto ARTG	30 May 2017
Number of TGA working days from submission dossier acceptance to registration decision *	225

* Target timeframe for standard applications: 220 working days

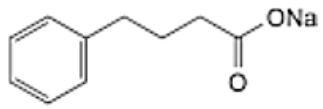
III. Quality findings

Introduction

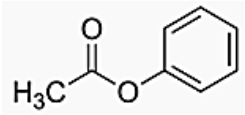
The sponsor has applied to register this new chemical entity as granules containing 84 g (483 mg/g) sodium phenylbutyrate in CRC HDPE bottles with desiccant PP cap. The bottle includes a calibrated measuring spoon (dispenses up to 3 g of sodium phenylbutyrate, in graduations of 250 mg) in the packaging.

The granules will be marketed under the trade name *Pheburane* granules.

Figure 3: Chemical structure of Sodium phenylbutyrate and Phenylacetate



Sodium phenylbutyrate



Phenylacetate

Phenylbutyrate is an aromatic short-chain fatty acid which is a chemical derivative of butyric acid naturally produced by colonic bacteria fermentation. Sodium phenylbutyrate is a pro-drug and is rapidly metabolised to phenylacetate (chemical structures above; see also Figure 2). Phenylbutyrate is rapidly converted via β-oxidation by medium chain acyl-CoA dehydrogenase to its active metabolite phenylacetic acid which is conjugated with glutamine to form phenylacetylglutamine, which is then excreted by the kidneys mediating waste nitrogen removal through urinary excretion. On a molar basis, phenylacetylglutamine is comparable to urea (each containing 2 moles of nitrogen) and therefore provides an alternate vehicle for waste nitrogen excretion.

The usual total daily dose of sodium phenylbutyrate is 450 to 600 mg/kg/day in neonates, infants and children weighing less than 20 kg and 9.9 to 13.0 g/m^2/day in children weighing more than 20 kg, for adolescents and adults (see Tables 1-2 above). The safety and efficacy of doses in excess of 20 g/day have not been established.

The PI states that the total daily dose should be divided into equal amounts and given with each meal or feeding (for example, 4 to 6 times per day in small children). The granules can be directly swallowed with a drink (water, fruit juices and protein free infant formulas) or sprinkled on to a spoonful of solid food (mashed potatoes or apple sauce); in this case, it is important that the *Pheburane* and food is taken immediately in order to preserve the taste-masking.

Instructions are included to administer only with the calibrated dosing spoon.

Instructions for administration by nasogastric or gastronomy tube are included in the PI (for dosing see Tables 3-4 above) and state that the granules should be prepared as a solution (50 mg/mL) by hospital or pharmacy for administration by these routes with purified water with the use of a syringe and rinsed with water. The PI includes instructions for preparation of the solution and storage conditions for the solution.

The effect of food on absorption is unknown.

Drug substance (active ingredient)

Sodium phenylbutyrate is a white or yellowish-white powder and freely soluble in water and in methanol, practically insoluble in methylene chloride.

Phenylbutyrate is known to be oxidised to phenylacetate which is enzymatically conjugated with glutamine to form phenylacetylglutamine in the liver and kidney. Phenylacetate is also hydrolysed by esterases in liver and blood.

Phenylbutyrate is rapidly absorbed under fasting conditions. After a single oral dose of 5 g of sodium phenylbutyrate, in the form of granules, measurable plasma levels of phenylbutyrate were detected 15 minutes after dosing. The mean time to peak concentration was 1 hour and the mean peak concentration 195 µg/mL. The elimination half-life was estimated to be 0.8 hours.

The volume of distribution of phenylbutyrate is 0.2 L/kg.

After a single dose of 5 g of sodium phenylbutyrate granules, measurable plasma levels of phenylacetate and phenylacetylglutamine were detected 30 and 60 minutes respectively after dosing. The mean time to peak concentration was 3.55 and 3.23 hours, respectively, and the mean peak concentrations (C_{max}) were 45.3 and 62.8 µg/mL respectively. The elimination half-life was estimated to be 1.3 and 2.4 hours, respectively.

Studies with high intravenous doses of phenylacetate showed non-linear pharmacokinetics characterised by saturable metabolism to phenylacetylglutamine. Repeated dosing with phenylacetate showed evidence of an induction of clearance.

In the majority of patients with urea cycle disorders or haemoglobinopathies receiving various doses of phenylbutyrate (300 to 650 mg/kg/day up to 20 g/day) no plasma level of phenylacetate could be detected after overnight fasting. In patients with impaired hepatic function the conversion of phenylacetate to phenylacetylglutamine may be relatively slower. Three cirrhotic patients (out of 6) who received repeated oral administration of sodium phenylbutyrate (20 g/day in three doses) showed sustained plasma levels of phenylacetate on the third day that were five times higher than those achieved after the first dose.

In normal volunteers gender differences were found in the pharmacokinetic parameters of phenylbutyrate and phenylacetate (area under the plasma concentration versus time curve (AUC) and C_{max} approximately 30 - 50 % greater in females), but not phenylacetylglutamine. This may be due to the lipophilicity of sodium phenylbutyrate and consequent differences in volume of distribution.

Approximately 80 to 100 % of the medicinal product is excreted by the kidneys within 24 h as the conjugated product, phenylacetylglutamine.

The partition coefficient ($LogP_{octanol/water}$) of sodium phenylbutyrate is 2.42 and the dissociation constant pKa is 4.76 (phenylbutyric acid). The active ingredient is hygroscopic. Sodium phenylbutyrate is freely soluble in water and in methanol, practically insoluble in methylene chloride and practically insoluble in acetone and diethyl ether. As sodium phenylbutyrate is freely soluble in water, particle size is not controlled. Sodium phenylbutyrate is achiral. The pH is 6.5 to 7.5 (0.2 g in 10 mL water). There are no known polymorphs of sodium phenylbutyrate.

It has an empirical formula of $C_{10}H_{11}NaO_2$ and a molecular weight of 186.2. It has a strong salty taste. Sodium phenylbutyrate is known chemically as 4-phenylbutyric acid, sodium salt. Structural characterisation was provided using appropriate methods.

The drug substance specification is according to the European Pharmacopeia (Ph.Eur.) monograph and includes tests and limits for Ph.Eur. impurities A (3-benzoylpropionic acid) and B (alpha tetralone). The limits for the each unspecified impurity are in line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) identification threshold.

The active substance specifications include tests for appearance, heavy metals, impurities, assay (, water content, pHand residual solvents. Impurities were described as per Ph. Eur.

Drug product

The proposed granules are sugar-coated spheres containing sodium phenylbutyrate. The granules are white to off-white granules, manufactured standard processes such as spray coating active ingredient on sugar pellets, coating and packaging. The process has been validated and in-process controls are adequate for the dose form. The particle size of the granulate is controlled.

The excipients are conventional and used to mask the unpleasant (bitter) taste. The excipients include: sugar spheres, hypromellose, macrogol 1500, povidone, and ethylcellulose.

The finished product specifications include tests for appearance, identification, assay, impurities, dissolution and microbial quality, residual solvent, density and water content. Assay limits are acceptable. Impurity limits have been qualified.

The dissolution profile of the batch used in the bioequivalence study was provided and considered acceptable.

The stability data provided supports a 36 month shelf life when stored below 30°C protected from light in the proposed packaging.

Biopharmaceutics

Study LUC1001

There is no Australian reference product. A single bioequivalence study (Study LUC1001) has been conducted following a single dose of 5 g of sodium phenylbutyrate for the proposed product compared to the European reference product Ammonaps (940 mg/g). The study title is *'An open-label, two-period crossover study to determine the BE of two formulations of a single dose of 5 grams of sodium phenylbutyrate granules and to compare the taste of these two formulations in healthy volunteers.'* Ammonaps is not registered in Australia so the sponsor requested that they supplement the bioequivalence study with evidence of the efficacy and safety of the innovator drug (Ammonaps) from the literature (as they do not have access to the initial Ammonaps application). The literature search strategy was developed in consultation with the TGA.

The study was an open-label, laboratory-blind, single-dose, randomised, two-period crossover study under fasting conditions. Subjects received 5.32 g uncoated granules of the reference product or 10.21 g of the coated granules of the test product with 240 mL water. The interval between doses was 7 days. This was a two-stage bioequivalence study: a first cohort of fourteen healthy, Caucasian, non-smoking male and female subjects was entered into the first stage of the study and randomised before Treatment period 1. Based on the results of the first cohort, the option of adding more subjects was not exercised as bioequivalence was demonstrated in the analysis of data obtained from 13 subjects of the first cohort.

Standardised meals were given during the study. Blood plasma samples were taken up to 16 h post-dose. Fourteen subjects (8 males and 6 females) were eligible to enter the study. One female subject was withdrawn from the study during Treatment period 1 due to an adverse event (vomiting). Thirteen subjects completed both treatment periods.

The mean (SD) C_{max}, AUC_{0-16} T_{max} and $t_{1/2}$ values for phenylbutyrate following administration of a single, 5 mg oral dose under fasted conditions are below.

Table 7: Single dose pharmacokinetic results

	Tmax (hrs)	C_{max} (µg/mL)	AUC_{0-t} (µg*hr/mL)	AUC_{0-inf} (µg*hr/mL)	$t_{1/2}$ (h)
Test Product B (N=13)	0.750	214.300	449.631	452.503	0.390
Reference Product A (N=13)	0.500	227.203	470.272	472.330	0.385

After single dose (2.5 g, n=2; 5 g, n= 21) under fasting conditions, phenylbutyrate was rapidly absorbed with measurable plasma levels 15 minutes after administration. Peak concentrations of approximately 1000 µmol/L were reached after 1 h. The elimination half-life was estimated to be 0.8 h. Measurable plasma levels of phenylacetate and phenylacetylglutamine were detected 30-60 min after oral dosing of phenylbutyrate (the mean peak concentration is 45.3 and 62.8 µg/mL, respectively). T_{max} increased with the dose of phenylbutyrate and was around 3.5 h for both metabolites after 5 g phenylbutyrate. Elimination half-lives were estimated to be 1.3 and 2.4 hours, respectively.

The geometric mean ratios and 90% confidence intervals (Treatment T/ Treatment R) for phenylbutyrate were C_{max} 94.32% (86.95 - 102.31%) and AUC_t 95.61% (90.34 - 11.19%). The 90% confidence intervals for AUC and C_{max} for the proposed product were within 80 to 125% range, indicating that the granules are bioequivalent to the European reference granules.

Absolute Bioavailability data were not provided in healthy subjects. This was a hybrid dossier, with literature relating to other pharmacokinetic information, including intravenous (IV) data for cancer patients, reviewed separately by the clinical evaluator.

Quality summary and conclusions

Registration of the product with respect to chemistry and quality control is recommended.

IV. Nonclinical findings

Introduction

General comments

The sponsor did not conduct any nonclinical studies to support this application. The nonclinical dossier was literature based and was claimed to be identical to literature included in the EU dossier for Pheburane (note that the European Medicines Agency (EMA) also took into account their earlier evaluation of Ammonaps when approving Pheburane).

The literature search submitted to the TGA and its associated inclusion criteria had some limitations, and on their own the results did not provide very much in the way of relevant information for evaluation of the nonclinical safety of Pheburane.

The most pertinent source of nonclinical data for the current application was based on the EMA evaluation reports for Ammonaps[1] and Pheburane[2] and FDA and EMA evaluation reports for Ravicti[3]. None of the original data were available to the TGA but the nonclinical evaluation reports based on these data include some experimental detail and an evaluation of the actual data. These reports are the main source of nonclinical data for the current application.

Despite the criticisms of the literature search strategy, the total dataset provided for evaluation is considered likely to be adequate for a substance that has been granted orphan status (based on unmet clinical need for a life threatening condition in a small number of patients) and has had extensive clinical use since the clinical dataset is likely to be more complete than for a new chemical entity.

The maximum proposed dose rate for sodium phenylbutyrate is the dose of 0.6 g/kg/day in a 20 kg infant (15.0 g/m2). It should be noted that the sodium intake associated with a daily dose of 20 g/day of sodium phenylbutyrate is 2.47 g/day. The proposed PI document includes an appropriate warning statement for susceptible patient groups.

Relevance of nonclinical data with glycerol phenylbutyrate

The active ingredient in Ravicti is GPB, a triglyceride containing three molecules of PBA linked to a glycerol backbone. GPB is hydrolysed by lipases in the gastrointestinal tract to glycerol and PBA following oral administration; PBA is then absorbed and metabolised to the active moiety, PAA, before being conjugated to form PAGN. Therefore GPB can be considered to be a derivative of sodium phenylbutyrate, and apart from the initial hydrolysis step, the two substances are expected to undergo identical metabolic transformation in humans as well as in the nonclinical species (Figure 4).

Differences in the toxicity profile between the two substances might be expected based on pharmacokinetic differences, as well as from the additional exposure to glycerol in the case of GPB and due to the increased sodium intake for sodium phenylbutyrate. In toxicokinetic studies, GPB could not be detected in plasma following its oral administration to rats and monkeys and this indicates that it undergoes very rapid hydrolysis to phenylbutyrate. The plasma T_{max} occurred slightly later and plasma exposures (based on C_{max} and AUC values) tended to be slightly lower in animals and adult UCD patients following GPB administration compared with an equivalent dose of sodium phenylbutyrate (not the proposed clinical formulation). However, the opposite was true for paediatric UCD patients and is suggestive of age-dependent differences in metabolism.

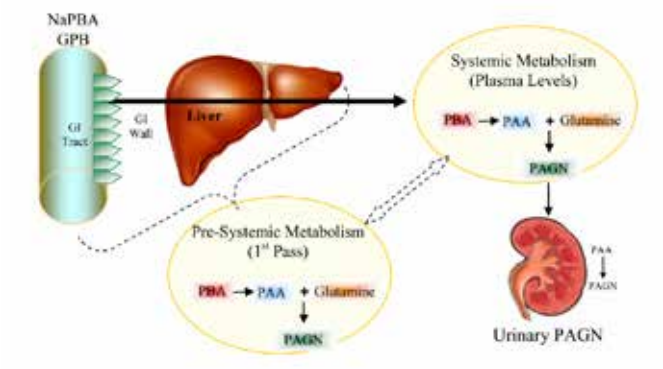
[1] EMA Initial scientific discussion for the approval of AMMONAPS; accessed on 7 July 2016; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000219/WC500024748.pd

[2] EMA Assessment report for PHEBURANE (21 February 2012); EMA/212039/2012; accessed on 7 July 2016; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002500/WC500147443.pdf

[3] FDA Pharmacology Review of RAVICTI, accessed on 7 July 2016; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000PharmR.pdf

[4] EMA Assessment report for RAVICTI, accessed on 9 August 2016; EMA/676925/2015; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003822/WC500199159.pd

Figure 4: Presystemic and systemic metabolism of glycerol phenylbutyrate (GPB) and sodium phenylbutyrate



PBA is released by dissolution of sodium phenylbutyrate or by pancreatic lipases via hydrolysis of GPB undergoes partial pre-systemic metabolism to PAA and/or PAGN in enterocytes and hepatocytes. Mokhtarani, M. et al (2012). Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders. Molecular Genetics and Metabolism 107(3): 308-14.

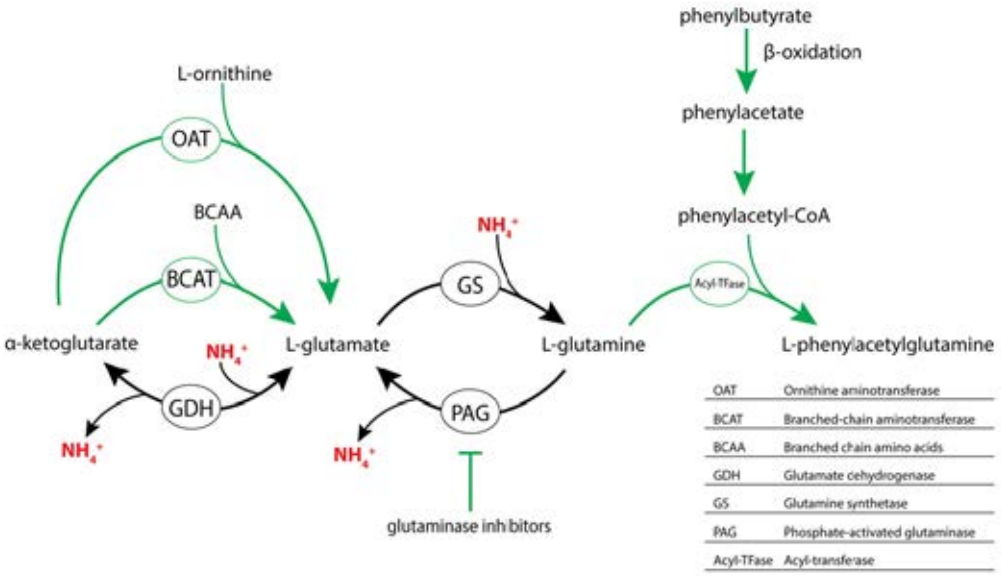
Pharmacology

Primary pharmacology

The sponsor has not submitted any primary pharmacology data to support the application. Sodium phenylbutyrate has been used clinically for many years in the treatment of UCDs to provide an alternate pathway to detoxify nitrogenous waste in combination with dietary protein restriction.[4] As shown in Figure 5, phenylbutyrate is a pro-drug for phenylacetate, which is able to conjugate glutamine through the action of phenylacetyl-CoA, and the resulting PAGN is subsequently excreted in urine.[5] Phenylacetylglutamine functions as a substitute for urea for the purposes of waste nitrogen excretion in man and higher primates. Sodium phenylbutyrate has been used to treat UCDs in the United States since 1987 (as an IND; approved as Buphenyl) and in Europe since 1999 (Ammonaps).

[4] Brusilow, S.W. (1991). Phenylacetylglutamine may replace urea as a vehicle for waste nitrogen excretion. Pediatric Research 29(2): 147-150.; Mistry, P.K. (2013). Rare disease clinical research network's urea cycle consortium delivers a successful clinical trial to improve alternate pathway therapy. Hepatology 57 (6): 2100-2.
Matoori, S. and Leroux, C. (2015). Recent advances in the treatment of hyperammonaemia. Advances Drug Delivery Reviews 90: 55-68 .
[5] Raper, H.S. and Wayne, E.J. (1928). A quantitative study of the oxidation of phenyl-fatty acids in the animal organism. Biochemical Journal 22: 188-197;
Quick, A.J. (1932). The relationship between chemical structure and physiological response. The conjugation of substituted benzoic acid. Journal of Biological Chemistry 96: 83-101;
James, M.O et al (1976). The conjugation of phenylacetic in man, sub-human primates and some non-primate species. Proceedings of the Royal Society of London B; 182: 23-35.
Webster, L.T. et al. (1976). Identification of separate acyl-CoA-glycine and acyl-CoA: L-glutamine-N-acyltransferase activities in mitochondrial fractions from liver of rhesus monkey and man. Journal of Biological Chemistry 251: 3352.

Figure 5: The role of phenylbutyrate as an ammonia scavenger in the treatment of UCDs



Glutamine synthesis in perivenous hepatocytes and skeletal muscle serves as an endogenous ammonia detoxification process, with glutamine acting as a transient metabolic ammonia sink. Phenylbutyrate acts as a pro-drug for phenylacetate, which is able to conjugate glutamine through the action of phenylacetyl-CoA. The resulting PAGN enhances glutamine elimination. Inhibitors of glutaminase may also be used therapeutically to increase glutamine elimination. Glutamine synthesis may be enhanced by providing substrates for glutamine synthetase, such as L-ornithine and branched chain amino acids (BCAA). Taken from Matoori, S. and Leroux, C. (2015). Recent advances in the treatment of hyperammonaemia. Advances Drug Delivery Reviews 90: 55-68.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic studies were performed with sodium phenylbutyrate or its metabolites. Literature studies and reviews[6] report that phenylbutyrate has a number of interesting pharmacodynamic properties including inhibition of histone deacetylase, an enzyme which is involved in epigenetic mechanisms for remodelling chromatin structure and controlling gene expression. Inhibition of histone deacetylase is associated with gene inactivation, which can modulate the expression of tumour-relevant genes controlling the cell cycle and apoptosis. On the basis of this activity, a large number of investigations in animals and man have provided evidence that phenylbutyrate and phenylacetate reduce proliferation and have anti-tumour activity in vitro and in vivo. It has also been suggested that modification of lipid metabolism (by an inhibitory action on mevalonate

[6]Gilbert, J. et al (2001). A Phase I dose escalation and bioavailability study of oral sodium phenylbutyrate in patients with refractory solid tumor malignancies. Clinical Cancer Research 7: 2292-2300.;
Kennedy, C. et al (2002). Cell proliferation in the normal mouse mammary gland and inhibition by phenylbutyrate. Molecular Cancer Therapeutics 1: 1025-1033.;
Perlmutter, D. (2002). Chemical chaperones: a pharmacological strategy for disorders of protein folding and trafficking. Pediatric Research 52: 832-6.;
Ma, X. et al (2009). Histone deacetylase inhibitors. Drugs 69(14): 1911-34.; Ricobaraza, A. et al (2009). Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer disease mouse model. Neuropsychopharmacology 34: 1721-32;
Iannitti, T. and Palmieri, B. (2011). Clinical and experimental applications of sodium phenylbutyrate. Drugs R D 11(3): 227-49; Zhou, W. et al (2011). Phenylbutyrate up-regulates the DJ-1 protein and protects neurons in cell culture and in animal models of Parkinsons disease. The Journal of Biological Chemistry 286(17): 14941-51.; Kusaczuk, M. et al (2015). Phenylbutyric acidL simple structure – multiple effects. Current Pharmaceutical Design 21: 2147-66.

decarboxylase) and activation of peroxisome proliferation activation receptors may contribute to these effects. Phenylbutyrate has also been shown to inhibit choline acetyltransferase, Dihydroxyphenylalanine (DOPA) and 5-hydroxytrptophan decarboxylases, and also Na/K/ATPase. The absence of formal secondary pharmacodynamic and toxicokinetic studies precludes any conclusions being drawn about possible secondary pharmacodynamic effects being encountered during the therapeutic use of sodium phenylbutyrate.

Phenylbutyrate has been investigated in a number of disorders associated with aberrant proteins, including sickle cell disease and thalassaemias as well as in cystic fibrosis, based on its ability to function as a molecular chaperone. In addition, phenylbutyrate has been investigated for potential efficacy in the treatment of motor neurone disorders, neurodegenerative diseases (including Huntingdon's disease, amyotrophic lateral sclerosis, Parkinson's and Alzheimer's diseases), inflammatory disorders, diabetes and obesity and ischaemic injury.

No safety pharmacology studies have been conducted with sodium phenylbutyrate but studies were conducted with GPB and its metabolites to support registration of Ravicti in the USA and Europe.[7]

Adverse CNS effects observed in a safety pharmacology study with GPB in cynomolgus monkeys following oral doses of 4 g/kg (48 g/m^2) included reduced locomotor activity, impaired balance and coordination and abnormal posture. Phenylbutyric acid (894 µg/mL) and PAA (988 µg/mL) inhibited potassium (hERG) currents by 36% and 54%, respectively. These concentrations are approximately 560 fold and 56 fold, respectively, their clinically observed unbound concentrations when adult UCD patients were treated with sodium phenylbutyrate (relative exposures in paediatric UCD patients were 1190 and 39, respectively). Phenylbutyric acid and PAA had no effects on delayed rectifier potassium currents in rabbit isolated cardiac myocytes at relative exposures of 995 and 17 for adults and 2122 and 12 in children (based on unbound C_{max}[8]).

Electrocardiogram (ECG) changes in conscious, unrestrained cynomolgus monkeys included significant prolongation of QTc interval[9] for at least 12 h after administration of GPB at oral doses of 4 g/kg. The increase in QTc was up to 25 ms (10.5%; $p<0.01$) in the first 2 h after administration. Additional significant ECG effects included decreased adjusted PR intervals and prolongation of QRS intervals but there was no effect on blood pressure and decreases in heart rate were minimal. There were no respiratory effects in monkeys at this dose level.

There were no toxicokinetic data accompanying the cardiovascular study in monkeys. The No observable effect level (NOEL) for the ECG effect was 1 g/kg. Using day 0 mean plasma C_{max} values for monkeys dosed at 1.1 g/kg for 12 months, the NOEL corresponds to relative exposures of approximately 1, 6 and 0.6 for PBA, PAA and PAGN, respectively based on data for sodium phenylbutyrate in adult UCD patients, and 2, 4 and 0.6,

[7] FDA Pharmacology Review of Raviciti, accessed on 7 July 2016; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000PharmR.p)
EMA Assessment report for Raviciti, accessed on 9 August 2016; EMA/676925/2015; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003822/WC500199159.pdf

[8] Assuming a clinical Cmax for PBA of 80.9 and 37.4 µg/mL (in adult and paediatric patients, respectively) and an unbound fraction of 2%; clinical Cmax for PAA of 52.2 and 75.1 µg/mL (in adult and paediatric patients, respectively) and an unbound fraction of 34%

[9] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

respectively in paediatric patients.[10] No toxicokinetic data are available for the GPB dose of 4 g/kg which was associated with QTc prolongation.

Based on the results of safety pharmacology studies with GPB and its metabolites, QT prolongation may be associated with doses in excess of those used clinically, although the toxicokinetic data in animals and humans are incomplete.

Pharmacokinetics

Data on the extent and speed of absorption of sodium phenylbutyrate in the nonclinical species were not provided, although a study in rats reported that systemic exposure of PBA and PAA were significantly higher following oral gavage doses of sodium phenylbutyrate compared with an equivalent dose of GPB.[11] However, absorption in animals is expected to be rapid and extensive. As already discussed, the parent compound could not be detected in plasma following oral administration of GPB to rats and monkeys, indicating that it is rapidly hydrolysed to phenylbutyrate. In a clinical study in advanced cancer patients the plasma T_{max} for PBA following ingestion of sodium phenylbutyrate tablets was 1.8 h, and mean oral bioavailability was 78%.[12] Phenylbutyrate pharmacokinetics were linear, and the apparent oral clearance was 15 L/h. Plasma concentrations of PAA and PAG exhibited Tmax values of 4.4 and 4.8 h, respectively.

PBA showed concentration-dependent binding, moderate to high in magnitude, to proteins in plasma of mouse, rat, rabbit, monkey and human. The free fraction increased with increasing concentration, and was 2-19% in plasma from humans. For PAA, a similar concentration dependence of low to moderate plasma protein binding was observed (37-66% in human plasma). For PAGN the extent of plasma protein binding was low (1.3-12%) in rats, monkeys and humans, and exhibited no concentration-dependent effects.[13] Tissue distribution of GPB and its metabolites was widespread following oral administration to monkeys, and there was no evidence of accumulation, although elimination from kidney, liver and more lipophilic tissues was slower than that from the systemic circulation. CNS exposure was reported to be limited in this species following GPB administration.[13] However, PAA has been shown to cross the blood-brain barrier in rats, and both phenylbutyrate and PAA were detected in the CSF of adult monkeys after IV administration. In neonatal rats, higher PAA exposure of CNS tissue was observed compared with adults, in which the blood: brain ratio was reported to be approximately 2, owing to the lack of PAA conversion to PAG in the immature animal.[14] The monkey data indicated that CNS penetration of both phenylbutyrate and PAA were high, as AUC values were higher for CSF than for plasma.

In all species PBA is converted via β-oxidation in the liver and most other organs to the active metabolite PAA. Phenylacetic acid may be hydrolysed via esterases in the liver and blood. However, in humans and higher primates, PAA is predominantly conjugated with glutamine (via glutamine N-acetyltransferase in the liver and kidney) to form PAGN. In addition, conjugation of phenylbutyrate with glutamine to form phenylbutyrylglutamine (PBGN) appears to be a relatively important metabolic pathway in both species. In lower

[10] Mokhtarani, M. et al (2012). Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders. Molecular Genetics and Metabolism 107(3): 308-14
[11] Kasumov, T. et al (2004). New secondary metabolites of phenylbutyrate in humans and rats. Drug Metabolism and Disposition 32(1): 10-19.
[12] Gilbert, J. et al (2001). A Phase I dose escalation and bioavailability study of oral sodium phenylbutyrate in patients with refractory solid tumor malignancies. Clinical Cancer Research 7: 2292-2300.
[13] EMA Assessment report for Raviciti, accessed on 9 August 2016; EMA/676925/2015; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003822/WC500199159.pdf
[14] Loo, Y.H. et al (1983). Experimental maternal phenylketonuria: an examination of two animal models. Dvelopmental Neuroscience 6: 227-34

mammalian species, PAA conjugates with glycine instead of glutamine to form PAG instead of PAGN.[15] Minor metabolites identified in a single study in rats and humans include intermediates in the β-oxidation of phenylbutyrate, including phenylacetone and 1-phenyl-2-propanol, and small amounts of glucuronidated metabolites. These authors reported that a substantial fraction of phenylbutyrate metabolites have not yet been identified in humans, highlighting a deficiency in current understanding of phenylbutyrate metabolism.[11]

Renal excretion accounted for approximately 80% of an oral dose of phenylbutyrate administered to monkeys, with only 0.87% recovered in faeces. Similarly, in humans, 80-100% of an oral dose of sodium phenylbutyrate was excreted by the kidneys within 24 h as PAGN.

Pharmacokinetic drug interactions

Both PBA and PAA showed some potential to reversibly inhibit cytochrome P450 (CYP) enzymes, albeit only at millimolar concentrations. The Ki for inhibition of human hepatic CYP1A2, CYP2C8 and CYP2C9 by PAA was reported to be 15.1 mM[16], which is of possible clinical relevance.[17] The EMA had requested the sponsor of Ravicti to investigate the potential of GPB to inhibit CYP2C9 in vivo4.Both PBA and PAA were reported to produce minimal in vitro induction of human hepatic CYP1A2 and CYP3A4/5.[16]

It has been reported in the literature that conjugated PAA is actively secreted by probenecid-sensitive renal organic anion transporters.[18] No formal investigations of potential pharmacokinetic interactions have been conducted, although ongoing studies of effects on P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3 and OCT1 were reported in the EMA evaluation of Ravicti.[13]

In summary, the available data indicate that the monkey is a suitable model for nonclinical studies with GPB, and based on their similarity, sodium phenylbutyrate, with the rat being of lesser value owing to the glycine conjugation pathway. Data on potential drug interactions based on interactions with transport proteins are inadequate.

Toxicology

Acute toxicity

Single dose toxicity studies with sodium phenylbutyrate were not submitted, but mortalities occurred following administration of single oral doses of 1.57 g/kg (9.4 g/m^2, or 0.5 times the maximum recommended human dose (MRHD)) in a micronucleus assay in rats.

The maximum tolerated dose (MTD) of GPB in rats was 0.9 g/kg/day (5.4 g/m^2). Signs of toxicity included hypoactivity, prostration, rigid muscle tone, impaired equilibrium and muscle coordination and gasping and laboured or shallow respiration, with death occurring at doses in excess of 1.2 g/kg. Monkeys were less sensitive to the toxic effects of GPB, with the MTD being in excess of 6.5 g/kg (>78 g/m^2). Clinical signs of treatment in

[15] James, M.O et al (1976). The conjugation of phenylacetic in man, sub-human primates and some non-primate species. Proceedings of the Royal Society of London B; 182: 23-35
[16] FDA Pharmacology Review of Raviciti, accessed on 7 July 2016; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203284Orig1s000PharmR.pdf
[17] Assuming a clinical Cmax of 75 µg/mL (in paediatric patients; Section 6.1.4) and 66% binding to plasma proteins, ratio of Ki to Cmax for unbound PAA, R = 8.0
[18] Pedemonte, W.A et al (1976). Penetration of phenylacetic acid across the blood-cerebrospinal fluid barrier. Research Communications in Chemical Pathology and Pharmacology 14(1): 111-6.

this species included mucoid or soft faeces, diarrhoea, emesis, hypoactivity and sleeping, and tremors.

Repeat-dose toxicity

There are no repeat dose toxicity data with sodium phenylbutyrate. As discussed, data from repeat-dose toxicity studies with GPB, submitted to the FDA and EMA[7] to support marketing applications for Ravicti can provide some indication of the potential toxicity of sodium phenylbutyrate. However, the data was not available for the TGA nonclinical evaluator to review and the FDA and EMA evaluation reports have some limitation in terms of the amount of detail provided. Good laboratory practice (GLP) compliant studies to support registration of Ravicti included a 13 week study in mice, studies of up to 26 weeks in rats, and up to 52 weeks in monkeys. Oral doses were administered once daily. Toxicokinetic studies reported plasma concentrations of the metabolites PAA, PAG (in rodents) and PAGN in monkeys.

Relative exposure

Exposure ratios for PBA and PAA have been calculated from the toxicokinetic studies conducted to support repeat-dose toxicity studies with GPB[16]. Human reference values are from a clinical study in adult and paediatric UCD patients[10] which provide mean plasma PBA and PAA exposures during treatment with clinical doses of sodium phenylbutyrate tablets. Hence the human data do not represent the maximum anticipated exposure with the MRHD of Pheburane granules. However, they are considered to be the most appropriate data set to use for the purposes of estimation of plasma exposures anticipated during clinical use.

The AUC data used for mouse and monkey is the mean of male and female values on the last sampling occasion, and was calculated on a different basis in each species, as indicated in the table legend, adding an additional degree of uncertainty. AUC data from the 26 week rat study have not been included in the table as it appears as if they may not have been reported correctly. Plasma AUC values were not provided for the mouse carcinogenicity study. In addition, the plasma AUC values in the 13 week mouse study were provided as a range, so relative exposures were calculated using the midpoint of this range. Despite all these uncertainties, the calculations provide a reasonable estimate of exposure levels for PBA and PAA in some of the repeat-dose toxicity studies with GPB, and hence provide an approximate indication of relative exposure during therapeutic use of sodium phenylbutyrate.

Relative exposures have also been calculated based on the combined AUCs for PBA and PAA, as per the FDA and EMA product information documents for GPB. This approach is probably appropriate given that the human AUCs for both are similar, and the moiety responsible for any toxicity cannot be known. The relative exposures for the parent compound were mostly subclinical, or up to 2 in the case of the 12 month monkey study for paediatric dosing. Exposures for the active metabolite PAA were low to adequate multiples of the anticipated clinical levels, being up to 4 in the 13 week mouse study, 8 and 15 for male and female rats respectively in the carcinogenicity study, and up to 12 in the 12 month monkey study. Relative exposures based on the sum of PBA and PAA exposures are correspondingly intermediate between the parent and active metabolite relative exposure levels.

Table 8: Relative exposure in repeat-dose toxicity and carcinogenicity studies with GPB[3]

Species	Study duration		Dose (g/kg /day)	AUC^ (µg.h/mL)			Exposure ratio#		
				PBA	PAA	PBA + PAA	PBA	PAA	PBA + PAA
Mouse (Crl:CD(ICR)	13 weeks (Day 90) 0-∞		0.65	127	957	1084	0.3 (0.5)	2 (1)	1.0 (1.1)
			0.9	176	1472	1548	0.3 (0.7)	2 (2)	1.4 (1.5)
			1.2	350	2407	2757	0.7 (1)	4 (3)	2.5 (2.7)
Rat (SD)	2 years carc) AUC all Day 364	M	0.07	26	64	90	0.05 (0.1)	0.1 (0.1)	0.1 (0.1)
			0.21	74	426	500	0.1 (0.3)	0.7 (0.6)	0.5 (0.5)
			0.65	138	4636	4774	0.3 (0.6)	8 (6)	4.3 (4.7)
		F	0.1	104	166	270	0.2 (0.4)	0.3 (0.2)	0.2 (0.3)
			0.3	233	1974	2207	0.5 (1)	3 (3)	2.0 (2.2)
			0.9	311	9074	9385	0.6 (1)	15 (12)	8.5 (9.3)
Monkey (Cynomolgus)	12 months (day 358)		0.7	496	1381	1877	1 (2)	2 (2)	1.7 (1.9)
			1.1	549	2499	3048	1 (2)	4 (3)	2.8 (3.0)
			1.5	569	7055	7624	1 (2)	12 (9)	6.9 (7.6)
Human UCD patients Mean data	Adults (n=44)		12.3 g/day	508	599	1107	–		
	Children (n=11;10.2 years)		10.9 g/day	236	773	1009			

= animal: adult human plasma AUC, with paediatric exposure ratio in parentheses; ^ = $AUC_{0-\infty}$ for mouse (using the midpoint of the AUC range; 'AUC_{all}' for the rat; AUC_{last} for monkey and AUC_{0-24h} for humans; data are for the sexes combined unless otherwise specified;

Major toxicities

As noted above, there are no repeat dose toxicity data for sodium phenylbutyrate. In repeat-dose toxicity studies with GPB the major target organs were the CNS, liver and haematopoietic system.

CNS effects

CNS toxicity was observed in repeat-dose studies with GPB in mice, rats and monkeys. In all three species hypoactivity, impaired equilibrium and shallow or laboured respiration were reported. Additional effects included ptosis in mice, rigid muscle tone in rats, and in monkeys, hunched posture, recumbency and tremor. Phenylacetate exposure of rats either in utero or in early postnatal life has been reported to be neurotoxic in literature studies. This is discussed below (see 'Reproductive toxicity' and 'Paediatric use').

Adverse CNS effects of sodium phenylbutyrate and PAA have been reported in clinical studies in patients with advanced cancer. Twice daily IV infusion of 60-360 mg/kg/day sodium phenylbutyrate was associated with short term memory loss, sedation and confusion.[19] Similarly, reversible effects reported following IV administration of PAA to cancer patients (125–150 mg/kg twice a day (BID)) included somnolence, fatigue, light-headedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy, associated with plasma PAA levels ranging from 499 to 1285 µg/mL.[20] Oral administration of sodium phenyl butyrate was also associated with CNS toxicity, with fatigue and neurocortical effects including slurred speech, decreased concentration and confusion reported following oral administration at doses of 9 to 45 g/kg/day in 3 divided doses.[12]

Liver

Chronic treatment of mice, rats and monkeys with GPB resulted in increased hepatic weight, and was associated with minimal to mild centrilobular hepatocellular hypertrophy in mice and monkeys. These changes are suggestive of hepatic enzyme induction. In a neonatal rat toxicity study, minimal to mild periductal mixed cellular infiltrates in liver were observed after 7 weeks of treatment with GPB. The EMA evaluator reported that these effects were considered by the sponsor to be an adaptive change occurring as a result of the metabolic process in which GPB is converted to PAA.

Haematopoietic system

Mild reductions in red cells, haemoglobin concentration, haematocrit and platelets were reported in the repeat-dose studies in rats and monkeys, in the absence of any histological correlates in bone marrow. Reduced thymic weight was reported in the 14 day study in rats, but not in longer duration studies. Small thymus size and histological evidence of minimal lymphoid depletion were reported in the 13 week study in monkeys dosed at 1.75 g/kg/day, and some females also exhibited enlarged and discoloured lymph nodes at this dose level.

Adverse effects of sodium

It is noted that the sodium intake associated with a daily dose of 20 g/day of sodium phenylbutyrate is 2.47 g/day. In clinical studies in advanced cancer patients the increased sodium load associated with sodium phenylbutyrate administration was associated with secondary peripheral oedema. The proposed Product Information document states that Pheburane should be used with extreme caution, if at all, in patients with cardiac or renal

[19] Camacho, L.H. et al (2007). Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumours. Investigational New Drugs 25: 131-8
[20] Thibault, A. et al (1995). Phase I study of phenylacetate administered twice daily to cancer patients. Cancer 75(12): 2932-8

dysfunction, and with care in patients who are on a controlled sodium diet or those with clinical conditions in which there is sodium retention with oedema.

Genotoxicity

An Ames test of limited validity (lacking the power to detect A-T and G-C base pair mutations) found no evidence of sodium phenylbutyrate mutagenicity.[21] However, neither sodium phenylbutyrate nor GPB were genotoxic in in vivo micronucleus assays in rats. In addition, the GPB metabolites PBA, PAA, PAGN and PAG were not genotoxic in the Ames test, and PAA, PAGN and PAG were negative in chromosomal aberration assays in Chinese hamster ovary (CHO) cells. Although phenylbutyric acid was clastogenic in CHO cells in the presence of metabolic activation, this occurred at potentially cytotoxic doses, and a second in vitro clastogenicity assay was conducted in human lymphocytes was negative. Overall there are sufficient data of adequate quality to make an assessment that sodium phenylbutyrate is not genotoxic.

Carcinogenicity

No carcinogenicity studies have been conducted with sodium phenylbutyrate. Glycerol phenylbutyrate was not carcinogenic in a 26 week study in hemizygous Tg.rasH2 mice, at oral doses of 600 and 1000 mg/kg/day. Average plasma concentrations of GPB metabolites PBA, PAA and PAG were reported in this study, corresponding to relative exposures of 0.08 to 0.2 for PBA and 0.6 to 10 for PAA. However, multiple tumours and pre-neoplastic changes were observed in the 2 year rat carcinogenicity assay with GPB doses of 70, 210 and 650 mg/kg/day in males, and 100, 300 and 900 mg/kg/day in females. Non-neoplastic findings in this study included focal hypertrophy in the adrenal cortex, pancreatic acinar cell hyperplasia, thyroid follicular cell hyperplasia, cystic endometrial hyperplasia of the uterus, Zymbal's gland hyperplasia, basophilic foci in the liver and retinal atrophy. Treatment associated tumours included pancreatic acinar cell adenoma and/or carcinoma in high dose (HD) males and females, Zymbal's gland carcinoma in mid dose (MD) and HD males and HD females, thyroid follicular cell adenoma in both sexes at the HD level, and combined follicular cell adenoma or carcinoma in HD females; combined adenoma or carcinoma in adrenal cortex in HD females, and uterine polyp and combined uterine polyp or sarcoma in HD females.

In the absence of positive genotoxicity findings with GPB and its metabolites, non-genotoxic mechanisms are likely to underlie the tumour findings in rats. Some of the tumour types observed are likely to be rodent-specific tumours of no relevance to humans. In the pancreas, acinar cell proliferation, adenoma and carcinoma were observed. Pancreatic acinar cell proliferation is considered to be unique in the rat and acinar cell hyperplasia and adenomas are not precursors of acinar cell carcinoma in humans.[13] If glycerol and butyrate influence the release of cholecystokinin, which is only mitogenic to rat pancreatic acinar cells, this may account for their stimulation and the progression to carcinoma. However, no mechanistic data are available to support of refute this hypothesis.

A possible non-genotoxic mechanism underlying the development of thyroid follicular cell tumours is through hepatic microsomal enzyme induction.[22] The GPB metabolites PBA and PAA induced cytochrome P450 enzymes in cultured human hepatocytes, and hepatocellular hypertrophy (indicative of enzyme induction) was observed in mice and

[21] EMA Initial scientific discussion for the approval of Ammonaps; accessed on 7 July 2016; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000219/WC500024748.pdf

[22] Capen (1997). Toxicologic Pathology: Nonclinical safety assessment. 25(1): pp 39-48. Ed Sahota, P.S., Popp, J.A., Hardisty, J.F. and Gopinath, C. CRC Press

monkeys in repeat-dose toxicity studies in these species. Hepatocellular hypertrophy was not observed in rats in repeat-dose studies with GPB but an increased liver weight is consistent with enzyme induction. Therefore, the weight of evidence from rats and other species suggests that the thyroid tumours in rats were secondary to hepatic enzyme induction, a mechanism that does not appear to be relevant to the risk of thyroid tumour development in humans. Again, adequate mechanistic data are not available to confirm or refute this hypothesis.

The relevance of positive carcinogenicity findings with GPB to the potential carcinogenicity of sodium phenylbutyrate is unknown. However, for reasons that have already been discussed above, the nonclinical studies with GPB have been accepted to be of direct relevance to the safety assessment of sodium phenylbutyrate. Therefore the carcinogenicity findings with GPB cannot be ignored. Pancreatic acinar cell adenoma, carcinoma and combined adenoma or carcinoma, were reported at relative exposures (based on combined exposures for PBA and PAA) of 4 and 9 in males and females, respectively. In females, thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp, and combined polyp or sarcoma were reported at relative exposures, based on combined AUCs for PBA and PAA, of 9.

The sponsor has cited evidence from the literature that sodium phenylbutyrate and PAA are cellular differentiating and cytostatic agents in vitro, and have anti-tumour effects including altered gene expression for tumour growth, invasion, angiogenesis and immunogenicity James et al, 1972[23]. Anti-tumour effects of sodium phenylbutyrate and PAA are proposed to be based on inhibition of histone deacetylase, hypomethylation, modification of lipid metabolism and activation of peroxisome proliferation receptors.[24] However, these activities do not preclude a carcinogenic effect of sodium phenylbutyrate or its metabolites during chronic administration. There have been literature reports of histone deacetylase down regulation being associated with certain human tumours, or with metastatic progression of human tumours, and the development of therapy-induced tumours in patients chronically treated with histone deacetylase inhibitors such as sodium phenylbutyrate cannot be excluded.[25]

Reproductive toxicity

Developmental toxicity has not been adequately investigated with sodium phenylbutyrate and its metabolites. However, studies with GPB complied with ICH guidelines[26] and EMA guidance[27] and were GLP compliant. There are no studies examining placental or lactational transfer of sodium phenylbutyrate, GPB or their metabolites.

A number of literature studies have provided evidence that phenylacetate is neurotoxic to rats following in utero or early post-partum exposure. These studies were not conducted under GLP conditions and the experimental protocols deviated significantly from the ICH guideline recommendations. They were designed to investigate cerebral lesions in the offspring of dams in an animal model for phenylketonuria. Maternal exposure to PAA by continuous SC infusion at levels yielding plasma PAA concentrations of 0.58 µmol/mL (91.6 µg/mL, less than 2-fold the plasma C_{max} in adult UCD patients) resulted in 100% fetal

[23] James MO, Smith RL, Williams RT and Reidenberg M (1972). The conjugation of phenylacetic acid in man, sub-human primates add some non-primate species. Proc R Soc Lond 182 :25-35
[24] Ma, X. et al (2009). Histone deacetylase inhibitors. Drugs 69(14): 1911-34.; Ricobaraza, A. et al (2009). Phenylbutyrate ameliorates cognitive deficit and reduces tau pathology in an Alzheimer disease mouse model. Neuropsychopharmacology 34: 1721-32;
[25] West, A.C. and Johnstone, R.W. (2016). New and emerging HDAC inhibitors for cancer treatment. Journal of Clinical Investigation 124(1): 30-9.
[26] ICH guidelines S5(R2)
[27] EMEA/CHMP/203927/2005

mortality. Reduced fetal body and cerebral hemisphere weights and learning deficits were associated with maternal plasma PAA concentrations of 0.33 µmol/mL (52.1 µg/mL, equivalent to the plasma C_{max} in adult UCD patients).[28] Hypoactivity and impaired performance in a learning task was reported following SC administration of PAA to newborn rats at doses up to 170 mg/kg/day from postnatal days 2-21, with neuroanatomical deficits including decreases in numbers of dendritic branching and delayed synaptic development in the brains of newborn rats receiving similar treatment. The EMA Summary of Medicinal Product Characteristics (SmPC) for Pheburane refers to these data in statements on use in Pregnancy and Lactation.

Relative exposure

Exposure ratios for PBA and PAA have been calculated from the toxicokinetic studies conducted to support embryofetal development studies with GPB.[16] Human reference values are from a clinical study in adult and paediatric UCD patients[10] which provide mean plasma PBA and PAA exposures during treatment with clinical doses of sodium phenylbutyrate tablets. Hence the human data do not represent the maximum anticipated exposure with the MRHD of Pheburane granules, although the MRHD has been included to allow relative exposures to be calculated based on dose per unit of body surface area. The AUC was calculated on a different basis in each species, as indicated in the table legend, adding an additional degree of uncertainty. Relative exposures have also been calculated based on the combined AUCs for PBA and PAA, as was done for the repeat-dose toxicity studies. Systemic exposures for PBA were up to 2 fold low the adult clinical exposure in the rat, and were a fraction of clinical exposures in the rabbit. Exposures for PAA were adequate multiples (up to 12-fold) of the adult clinical exposure in the rat, and up to 4 fold in the rabbit. Exposures based on combined AUCs for PBA and PAA were in between those for parent and active metabolite. Estimating relative exposures on an mg/m^2 basis appears to result in significant underestimation of systemic exposure.

Table 9: Relative exposure in reproductive toxicity studies with GPB

Species	Daily dose		AUC^ (µg·h/mL)			Exposure ratio#			
	g/kg	mg/m^2	PBA	PAA	PBA + PAA	PBA	PAA	PBA + PAA	mg/m^2
Rat (SD) GD7	0.3	1.8	419	4244	4663	0.8 (2)	7 (5)	4.2 (4.6)	0.12
	0.65	3.9	873	5172	6045	2 (4)	9 (7)	5.5 (6.0)	0.26
	0.9	5.4	1198	7192	8390	2 (5)	12 (9)	7.6 (8.3)	0.36
Rabbit (NZW) GD19	0.15	1.8	31.5	873	904.5	0.06 (0.1)	1 (1)	0.8 (0.9)	0.12
	0.25	3	62.5	1556	1618.5	0.1 (0.3)	3 (2)	1.5 (1.6)	0.20
	0.35	4.2	49.4	2298	2347.4	0.1 (0.2)	4 (3)	2.1 (2.3)	0.28

Loo, Y.H. et al (1983). Experimental maternal phenylketonuria: an examination of two animal models. Dvelopmental Neuroscience 6: 227-34.

Species	Daily dose	AUC^ (µg·h/mL)			Exposure ratio#
Human (UCD patients)	**g/day**				-
Adults (*n*=44)	12.3	8.1	508	599	1107
Children (*n*=11; 10.2 years)	10.9	9.0	236	773	1009
MRHD	12	15.0	-		

= animal: adult human plasma AUC, with paediatric exposure ratio in parentheses; ^ = 'AUC_{all}' for the rat and rabbit; $AUC_{0\text{-}24h}$ for humans

Although GPB did not have an adverse effect on male or female fertility or reproductive function, there was a dose-dependent increase in embryolethality which was statistically significant at 1.2 g/kg/day. The NOEL of 0.9 mg.kg/day corresponds to relative exposures of approximately 2 and 12 for PBA and PAA, respectively, or approximately 8 for combined PBA and PAA, based on toxicokinetic data from the rat teratology study.

There was no adverse effect on embryo viability when dams were treated during the period of organogenesis, although maternal toxicity was associated with reduced fetal weight. Fetuses of treated dams exhibited a wide range of abnormalities, including absence of anal opening, short or thread-like tail and undescended testes, and there were increased numbers of fetuses with skeletal variations and incomplete ossifications (delayed or incomplete ossification of skull, vertebrae, ribs, sternum, forelimbs and pelvis). While the total number of abnormal fetuses was significantly increased with maternal dosing at 0.65 g/kg/day and above, there was no single type of malformation that showed a statistically significant increase in frequency.

The NOEL for fetal abnormalities was 0.3 g/kg/day, which corresponds to relative exposures of approximately 1 and 7 for PBA and PAA, respectively, or approximately 4 for combined PBA and PAA. Fetal anomalies were also observed in a study examining GPB toxicity in juvenile rats (see below, 'Paediatric use'). Umbilical hernia, limb or digit abnormalities, gastroschisis, tail anomalies and absence of anal opening were seen in the offspring of rats treated orally with GPB at doses of 0.9 g/kg/day and above from the second day of birth through mating and pregnancy to postnatal day 20. The NOEL of 0.65 mg/kg/day corresponds to relative exposures of approximately 2 and 9 for PBA and PAA, respectively, or approximately 6 for combined PBA and PAA. Thus a non-specific increase in developmental abnormalities was consistently observed in two separate studies at similar exposures.

Although no adverse fetal effects were observed in the rabbit teratology study, the maximum relative exposure levels (for PBA and PAA) were subclinical (although relative exposure was 2 for combined PBA and PAA). No maternal toxicity was reported, indicating that the MTD had probably not been achieved.

In contrast with the neurotoxicity reported in rats exposed to PAA in utero or in early postnatal life (described above), there were no adverse effects noted in standard tests for learning and memory in pups whose dams were dosed orally with GPB from gestation day 7 through to day 20 of lactation at doses up to 0.9 g/kg/day (to relative exposures of

approximately 2 and 12 for PBA and PAA, respectively, or approximately 8 for combined PBA and PAA). The F1 (next) generation was also reported to exhibit normal sexual maturation, mating and fertility, pregnancy and necropsy findings. Using the toxicokinetic data from the rat teratology study, the estimated maternal PAA exposure in this study was 7192 µg.h/mL, which is almost six times higher than the maternal exposures reported to be associated with neurotoxicity in the offspring. The explanation for the different neonatal outcomes is unclear.

The sponsor has proposed to refer to the neurotoxic effect of prenatal PAA exposure in the Product Information document. Although the studies with GPB do provide some degree of reassurance of a lack of potential for neurotoxicity (sufficient for the FDA not to refer to this effect in their Product Information document for Ravicti), based on the absence of any dedicated reproductive toxicity studies with sodium phenylbutyrate, reference to the neurotoxic effect of PAA is appropriate. However, data from reproductive toxicity studies with GPB should also be referred to.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.[29]

Although no reproductive toxicity studies have been conducted with sodium phenylbutyrate, there were adverse findings in the studies with GPB submitted to the FDA and EMA to support the registration of Ravicti, and the sponsor has proposed to refer to the neurotoxic effects associated with prenatal exposure to PAA reported in the Product Information document. In addition, the developmental toxicity findings referred to above are not consistent with a Category of B2. A Pregnancy Category of B3 is more appropriate.[30]

It is noted that pregnancy is a contraindication in the proposed Product Information document, and thus it appears that there are some contradictions to be resolved with respect to use in pregnancy.

Impurities

The proposed specifications for impurities in the drug product are below the ICH qualification thresholds.

Paediatric use

Pheburane is indicated for used in patients of all ages, including neonates. As discussed above ('Reproductive Toxicity'), a number of literature studies have provided evidence that PAA is neurotoxic to neonatal rats. While no data are available with sodium phenylbutyrate, a study in neonatal rats treated orally with GPB was submitted to the FDA and EMA to support the application for Ravicti. This study was in two parts. The first part was a general juvenile toxicity study in which pups were dosed from postnatal day 2 for seven weeks at up to 1.2 g/kg/day and found similar toxicities to those reported in adults. In the second part of the study, dosing was continued through mating on postnatal day 96

[29] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

[30] Category B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

to 100 through until 20 days post-partum. This study found no adverse effect on behaviour, including in standard tests of learning and memory, again in contrast to the effects of parenteral PAA administration on juvenile rats in literature studies. Although oral treatment of juvenile rats with GPB had no adverse effects on mating or fertility, doses of 0.9 g/kg/day and above were associated with reduced fetal survival (due to significant increases in resorptions), resulting in reduced numbers of live foetuses. In addition, the fetal anomalies were observed at doses of 0.9 g/kg/day and above, including umbilical hernia, limb or digit abnormalities, gastroschisis, tail anomalies and absence of anal opening. The studies in juvenile rats are supportive of the proposed paediatric dosing with sodium phenylbutyrate. The adverse developmental effects in the F1 generation are indicative of nonspecific developmental toxicity for GPB or its metabolites. No toxicokinetic data were available for this study but a similar dose administered in the main rat teratology study was associated with relative exposures of 4 and 7 for PBA and PAA, respectively.

Nonclinical summary and conclusions

- The nonclinical submission was a literature based submission. Of greatest relevance were the EMA evaluation reports for Ammonaps and Pheburane and FDA and EMA evaluation reports for Ravicti (glycerol phenylbutyrate; GPB), although none of the original data were available to the TGA. Despite the limitations in the total dataset provided for evaluation, it may be adequate for a substance intended for a life threatening condition which has had extensive clinical use, since the clinical dataset is likely to be more complete than for a new chemical entity.
- No nonclinical pharmacology data are available. Phenylbutyrate is a pro-drug for PAA, which is able to conjugate glutamine through the action of phenylacetyl-CoA, and the resulting PAGN is subsequently excreted in urine. Phenylacetylglutamine functions as a substitute for urea for the purposes of waste nitrogen excretion in man and higher primates.
- Overseas evaluations of data submitted to support registration of Ravicti may be acceptable to support the current application since GPB is a derivative of sodium phenylbutyrate, consisting of three molecules of PBA linked to a glycerol backbone. It is rapidly hydrolysed to glycerol and PBA following oral administration. Apart from the initial hydrolysis step and the presence of glycerol or sodium, GPB and sodium phenylbutyrate are expected to undergo identical metabolic transformation in humans as well as in the nonclinical species, and therefore nonclinical studies with GPB are of considerable relevance for the nonclinical assessment of Pheburane.
- Pharmacological properties reported in literature studies include inhibition of histone deacetylase, mevalonate decarboxylase, choline acetyltransferase, DOPA and 5-hydroxytrptophan decarboxylases, and also Na/K/ATPase, and the ability to act as a molecular chaperone. Based on some of these properties clinical studies have examined therapeutic potential in a wide range of diseases and disorders, including cancer, sickle cell disease, thalassaemias, cystic fibrosis, motor neurone disorders and neurodegenerative diseases, inflammatory disorders, diabetes and obesity and ischaemic injury.
- No safety pharmacology studies have been conducted with sodium phenylbutyrate. Adverse CNS effects observed in a safety pharmacology study with GPB in cynomolgus monkeys included reduced locomotor activity, impaired balance and coordination and abnormal posture. Inhibition of hERG currents was reported with PBA and PAA concentrations that were 560 fold and 56 fold, respectively, the clinically observed unbound levels in adult UCD patients. Significant prolongation of QTc interval (up to

25 ms) was reported in conscious, unrestrained cynomolgus monkeys with oral GPB doses of 4 g/kg. The clinical relevance for Pheburane is unknown.

- No nonclinical pharmacokinetic studies have been conducted with Pheburane. The pharmacokinetic profile of GPB in monkeys, and to a lesser extent in mice and rats, was similar to that in humans. Tissue distribution of GPB metabolites was widespread following oral administration to monkeys. Significant CNS exposure to phenylbutyrate and PAA was observed in monkeys following IV administration of sodium phenylbutyrate, and in rats following subcutaneous (SC) administration of PAA. Plasma protein binding of PBA and PAA was concentration-dependent in animals and humans (81 to 98% and 37 to 66%, respectively), while binding for PAGN was only 1.3 to 12% and did not show concentration-dependence.
- In all species phenylbutyrate undergoes β-oxidation in the liver and most other organs to the active metabolite PAA, which may be hydrolysed via esterases in the liver and blood. In humans and higher primates, PAA is predominantly conjugated to phenylacetylglutamine (PAGN) in the liver and kidney, but in lower mammalian species, conjugation is to glycine instead. Excretion is predominantly renal in animals and humans.
- PAA inhibition of human hepatic CYP1A2, CYP2C8 and CYP2C9 in vitro is of possible clinical relevance. Both PBA and PAA showed minimal potential for induction of human hepatic CYP1A2 and CYP3A4/5. PAA is actively secreted by probenecid-sensitive renal organic anion transporters. No formal investigations of potential pharmacokinetic interactions have been conducted.
- Oral sodium phenylbutyrate administration to rats caused mortalities in a micronucleus assay. Toxic effects included hypoactivity, prostration, rigid muscle tone, impaired equilibrium and muscle coordination and gasping and laboured or shallow respiration. The related substance GPB showed moderate to high toxicity in the monkey, associated with mucoid or soft faeces, diarrhoea, emesis, hypoactivity and sleeping, and tremors.
- There are no repeat dose toxicity data for sodium phenylbutyrate. In repeat-dose toxicity studies with GPB in mice, rats and monkeys the major target organ was the CNS, with signs of toxicity including hypoactivity, impaired equilibrium, shallow or laboured respiration, ptosis in mice, rigid muscle tone in rats, and in monkeys, hunched posture, recumbency and tremor. Plasma concentrations of PBA and PAA in these studies were low multiples of those anticipated with therapeutic use of Pheburane. In literature studies, PAA exposure of rats either in utero or in early postnatal life has been reported to be neurotoxic. Hepatic toxicity in studies with GPB included increased hepatic weight, with minimal to mild centrilobular hepatocellular suggestive of hepatic enzyme induction. Haematopoietic system effects in rats and monkeys were mainly limited to mild reductions in red cell parameters.
- Overall there are sufficient data of adequate quality to make an assessment that sodium phenylbutyrate and its metabolites are not genotoxic. There are no carcinogenicity data with sodium phenylbutyrate. Studies with GPB found no evidence of tumour formation in a transgenic mouse model, but there were multiple pre-neoplastic lesions and tumours in adrenal gland, pancreas, thyroid, uterus, Zymbal's gland and cervix in a standard 2 year carcinogenicity assay in the rat. The lowest observable effect level (LOEL) for these effects corresponded to a combined PBA and PAA relative exposure of 4 to 9.
- Developmental toxicity has not been adequately investigated with sodium phenylbutyrate and its metabolites, and there are no studies examining placental or lactational transfer of sodium phenylbutyrate, GPB or their metabolites. In a rat experimental model of maternal phenylketonuria, phenylacetate was neurotoxic

following in utero or early post-partum exposure, resulting in reduced fetal body and brain weight, impaired performance in learning and memory tasks and neuroanatomical deficits including decreased dendritic branching and delayed synaptic development. However, similar effects were not observed in GLP compliant dedicated reproductive toxicity studies with GPB, including a peri-postnatal toxicity study and a juvenile toxicity study.

- GPB reduced embryo survival in a fertility study in male and female rats in which dams were dosed up until gestation day 7 (NOEL at combined PBA and PAA relative exposures of approximately 8). Maternal treatment during organogenesis in this species was associated with reduced fetal weight and increases in skeletal variations and incomplete ossifications (combined relative exposures for PBA and PAA of 6). In addition, a wide range of abnormalities was seen, including absence of anal opening, short or thread-like tail, and undescended testes, but none showed a statistically significant increase in frequency. The NOEL for these effects corresponded to a combined relative exposure level for PBA and PAA of approximately 4. Umbilical hernia, limb or digit abnormalities, gastroschisis, tail anomalies and absence of anal opening were also seen in the offspring of rats treated orally with GPB at doses of 0.9 g/kg/day and above from the second day of birth through mating and pregnancy to postnatal day 20 (as part of a juvenile toxicity study). No adverse fetal effects were observed in a rabbit teratology study with GPB at a combined relative exposure level for PBA and PAA of up to 2.
- A juvenile toxicity study in neonatal rats treated orally with GPB found toxicities were comparable to those seen in adults following oral administration at doses up to 1.2 g/kg/day for 7 weeks. In a separate study, continued dosing through mating on postnatal day 96-100 through until 20 days post-partum resulted in reduced fetal survival and the fetal anomalies described above.

Nonclinical conclusions and recommendation

- The literature based submission, which included EMA evaluation reports for Ammonaps and Pheburane and FDA and EMA evaluation reports for Ravicti (glycerol phenylbutyrate; GPB). None of the original data with GPB were available to the TGA. The data set had a number of deficiencies and limitations.
- Prolongation of QTc interval in conscious monkeys treated orally with GPB is of possible clinical relevance for Pheburane.
- In vitro pharmacokinetic interaction data with sodium phenylbutyrate are inadequate.
- The CNS was the main target for GPB toxicity in safety pharmacology and repeat dose toxicity studies in mice, rats and monkeys. Hypoactivity, impaired equilibrium, shallow or laboured respiration, ptosis in mice, rigid muscle tone in rats, and in monkeys, hunched posture, recumbency and tremor are of potential clinical relevance.
- Sodium phenylbutyrate and its metabolites are not genotoxic. GPB showed no evidence of carcinogenicity in a transgenic mouse model but there were multiple pre-neoplastic lesions and tumours in adrenal gland, pancreas, thyroid, uterus, Zymbal's gland and cervix in a standard 2 year carcinogenicity assay in the rat.
- Using a rat experimental model of maternal phenylketonuria, phenylacetate was neurotoxic following in utero or early post-partum exposure, resulting in reduced fetal brain weight, impaired performance in learning and memory tasks and neuroanatomical deficits. However, similar effects were not observed in GLP compliant dedicated reproductive toxicity studies with GPB, including a peri-postnatal toxicity study and a juvenile toxicity study.

- Maternal treatment with GPB during early pregnancy reduced embryo survival in a fertility study and also in a juvenile toxicity study. Maternal treatment during organogenesis was associated with reduced fetal weight and increases in skeletal variations and incomplete ossifications. A non-specific increase in developmental abnormalities was seen in rats whose dams were dosed with GPB during organogenesis.
- A two-part juvenile toxicity study with GPB in neonatal rats was supportive of the proposed paediatric use of sodium phenylbutyrate.
- The nonclinical submission had significant deficiencies in terms of the quality and quantity of data to support the proposed application. However, this may be acceptable for a substance which has had extensive clinical use and is intended for a life threatening condition.
- There are some deficiencies in the nonclinical part of the safety specification.
- The sponsor did not make any comments on proposed changes to the Product Information document provided in the first round nonclinical evaluation report. The draft Product Information should be amended as directed (the details which are beyond the scope of this AusPAR).

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The submission gives a clear rationale for the development of Pheburane. As described below, Ammonaps was the original formulation of sodium phenylbutyrate used for the treatment of urea cycle defects (UCDs) as a nitrogen scavenger. However, Ammonaps has an objectionable taste and this resulted in poor compliance and potentially poor outcomes in the treatment of UCDs. Pheburane was developed as an encapsulated version of sodium phenylbutyrate which avoided the taste but did not alter the bioavailability of the medicine.

Alternate pathways of nitrogen waste excretion

The existence of such potentially useful pathways exist was shown one century ago[31] via the stoichiometric relationship between the administration of benzoate or phenylacetic acid and the resulting decreased urea nitrogen excretion, accounted for by the respective appearance of hippurate nitrogen and phenylacetylglutamine nitrogen in the urine. It was suggested that these pathways may be useful in patients with defective ureagenesis where the amino acid acylation products (hippurate and phenylacetylglutamine) may substitute for urea nitrogen excretion in all UCD. To date, however, they have been mostly used in CPS-I, OTC and ASS.[32]

[31] Lewis HB (1914) Studies in the synthesis of hippuric acid in the animal organism. J Biol Chem 18: 225–231. Sherwin et al., J. Biol. Chem., (1919), 40: 259-263.
[32] Brusilow, S., et al., "Amino Acid Acylation: a Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," Science 207:659-661 (1980).

Since phenylacetate has an offensive odour, sodium phenylbutyrate was developed. This compound was selected as it is rapidly oxidised in vivo to phenylacetate but has a less offensive odour. Sodium phenylbutyrate had been used since 1987 under an IND. Two presentations (both uncoated) are available: 500 mg tablets and powder/granules 94% weight/weight. Granules are usually prescribed in infants and children and in adults when large dose is required. Pheburane was developed as a hybrid generic formulation of the granule presentation of Ammonaps.

Pheburane granules

Bad taste or taste aversion are amongst the most frequent adverse events (AE) reported with Ammonaps. Moreover, this very bitter taste cannot be easily disguised and dietician support is often necessary.[33]

Sodium phenylbutyrate is notoriously bitter and in patients in whom it cannot be tolerated the medication has to be administered via nasogastric tube or gastrostomy.[34] In children, extemporaneously prepared sweetened suspensions of the oral powder may be needed in an effort to improve compliance.[35]

Rejection of unpalatable medications is a reflection of basic biology. From an evolutionary perspective, the senses that evaluate what is put into the mouth have evolved to reject that which is harmful and seek out that which is beneficial. Particularly, rejection of bitter-tasting and irritating substances is thought to have evolved to protect the animal from being poisoned and the plant producing these chemicals from being eaten. Moreover, bitter compounds stimulate rejection reflexes such as nausea and vomiting and children are more sensitive to bitter taste than adults.[36]

Since Ammonaps granules have an offensive taste the sponsor has developed an improved granule of sodium phenylbutyrate whereby coating of individual granules results in a formulation which has no immediate taste (that is, when swallowing the drug). The active ingredient remains sodium phenylbutyrate therefore, it was essential that the new product be bioequivalent to the reference product, which was subsequently demonstrated.

The background information is adequate to explain the proposed indications, the development of Pheburane and the rationale for the current hybrid application.

Guidance

The sponsor, in consultation with the TGA, developed a hybrid application and has relied upon specific TGA guidance on the development and presentation of the literature based section of the application.

[33] Guffon N. et al, Developing a new formulation of sodium phenylbutyrate Archives of Disease in Childhood (2012) 97:1081-85

[34] Brusilow SW, Maestri NE: Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr 1996; 43: 127-70

[35] Caruthers RL, Johnson CE 2007. Stability of extemporaneously prepared sodium phenylbutyrate oral suspensions. Am J Health Syst Pharm 64(14):1513-1515.

[36] Menella J, Beauchamp G: Optimizing Oral Medications for Children. Clin Ther 2008; 30: 2120-213

Contents of the clinical dossier

The clinical dossier contained the following:

- 1 bioequivalence study
- 14 Literature based study reports relating to pharmacokinetics, efficacy and safety
- 69 Clinical references
- The First EU Periodic benefit-risk evaluation report (PBRER), 2016

Paediatric data

Paediatric data are included in several of the submitted papers on the efficacy of sodium phenylbutyrate. There is no separate commentary about the use of sodium phenylbutyrate in children and the data are pooled with the adult data.

There is one specific study that includes data on the use of Pheburane in children.[37] This was a follow-up study of a French premarketing authorisation.

- *The sponsor should provide a separate commentary about the use of sodium phenylbutyrate in children*.

Good clinical practice

The submitted application stated the following:

> *Ethics Certification*
>
> The key clinical studies of sodium phenylbutyrate versus GPB were conducted by the same USA study group and the National Urea Cycle Disorders Foundation in a multi-centre collaboration across many US investigative centres. Studies were conducted around 2009 to 2012 and ethics certification and informed consent were all in line with ICH GCP Guidelines for these USA multicentre trials.
>
> All protocols were conducted under a US IND and were reviewed and approved by the appropriate Institutional Review Board. A Data Safety Monitoring Board was engaged throughout the studies and reviewed all safety results periodically. All patients or their parents signed a consent or assent form, which had been approved by local Institutional Review Boards, prior to enrolment and initiation of any protocol-specific activities

- *The clinical evaluator was unable to verify that all of the presented data complied with GCP.*

Evaluator's commentary on the clinical dossier

The dossier was poorly constructed and difficult to follow. All of the appropriate papers except one were included in the dossier. The PDF links from the table of contents in the dossier did not always function correctly and the appropriate paper had to be sourced manually through searching the files.

[37] Kibleur Y.A. Dobbelaere D. Barth M. Brassier A. Guffon N. Results from a nationwide cohort temporary utilization authorization (ATU) survey of patients in France treated with Pheburane (sodium phenylbutyrate) taste-masked granules. Journal of Inherited Metabolic Disease (2014) 37:1 SUPPL. 1 (S81).

Pharmacokinetics

Studies providing pharmacokinetic information

The following table describes the Pharmacokinetics (PK) studies submitted:

Table 10: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence †- Single dose	LUC1001 (Guffon 2012)	*
	Target population § - Multi-dose	Gilbert 2001 Lee 2010 Smith 2013	
Population PK analyses	Target population	Monteleone 2102 Mokhtaraini 2012	* *

* Indicates the primary PK aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of Pheburane is described through the following:

- A single bioequivalence study demonstrating that Pheburane was developed as a hybrid generic formulation of the granule presentation of Ammonaps.
- A series of literature articles describing the pharmacokinetics of sodium phenylbutyrate, often in comparator trials with glycerol phenylbutyrate.
- Some literature articles including higher doses used in the treatment of malignancies.

There were no dose finding studies presented. There were higher doses used in the treatment of malignancies suggesting linear pharmacokinetics up to about 36 g per day.[12]

There are significant deficiencies in the presented pharmacokinetic data that need to be addressed

- *Clarify the proposed dosing schedule and linearity of Pheburane.*
- *Clarify that the form of sodium phenylbutyrate used in all of the pharmacokinetic studies was the same the innovator product (Ammonaps) from the bioequivalence study.*
- *Demonstration that the dosing of Pheburane can be scaled by weight and surface area as in the proposed dosing schedule.*
- *Explain the dose-ranging in the proposed dosing schedule.*

Pharmacodynamics

Studies providing pharmacodynamic data

Following oral administration, sodium phenylbutyrate is metabolised by β-oxidation in the liver into phenylacetate which is rapidly converted to its CoA ester, phenylacetyl-CoA. The latter compound is conjugated to glutamine to form phenylacetylglutamine, which is excreted by the kidney. Glutamine (and therefore phenylacetylglutamine) contains 2 waste nitrogen atoms, so 2 moles of nitrogen are removed for each mole of sodium phenylbutyrate administered.[38]

Studies providing pharmacodynamic information

The following pharmacodynamic studies were submitted.

Table 11: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on PD Ammonia	Lee 2010 Brusilow 1993	

Brusilow 1993

Brusilow SW, Valle DL, Batshaw M. New pathways of nitrogen excretion in inborn errors of urea synthesis. Lancet 1979; 2:452-4

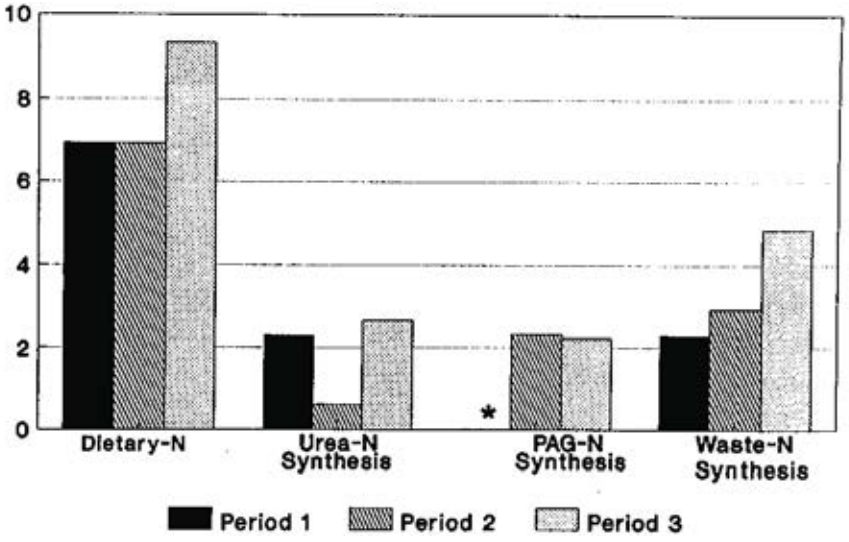
Net urea synthesis was evaluated in one 38-year old OTC patient treated with 16.5 g phenylbutyrate over three 3-day periods. In a first control period the patient received a fixed nitrogen intake (low protein diet only 120 g plus citrulline); in period II, 49.5 g sodium phenylbutyrate was added; and in period III, an additional 45 g of dietary protein (7.2 g nitrogen) was added. The results are given in Figure 6 and Table 12.

Table 12: Net urea synthesis in a 38-year old man with OTC deficiency during three 3-day periods

	Dietary N, g/3d	PAG-N, g/3d	Net Urea Synthesis g/3d
Period I	20.8	0	6.85
Period II	20.8	6.97	1.83
Period III	28.0	6.67	7.95

[38] Batshaw ML, Macarthur RB, Tuchman M: Alternative pathway therapy for urea cycle disorders: Twenty years later; J Pediatr 2001 (138); 1 Pt 2: S46-S55

Figure 6: Pharmacodynamics of phenylbutyrate in 1 OTC adult patient



Evaluator's conclusions on pharmacodynamics

There were literature based data to support the proposed mechanism of action of sodium phenylbutyrate, acting via its active metabolite phenylacetic acid, as an alternate pathway for the excretion of excess nitrogen. Brusilow 1993 did demonstrate increased nitrogen excretion in a single patient after receiving sodium phenylbutyrate.

- *The sponsor should reinvestigate the literature for further evidence of a dose response effect on nitrogen excretion with sodium phenylbutyrate.*

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

The dossier states that there is no dose finding information. The submission includes the following justification for the dosing regimen.

> No dose-finding study has been performed in UCD patients. The proposed daily dosage was derived on the basis that one mole of phenylbutyrate will be metabolised to one mole of phenylacetylglutamine, and from the estimated nitrogen to be excreted on a restricted protein intake. On a molar basis phenylacetylglutamine is comparable to urea (each containing two nitrogen atoms) and provides therefore an alternate vehicle for waste nitrogen disposal. Children (6-24 months of age) receiving a diet of 0.2 g/kg/d of nitrogen (1.25 g/kg/d of protein) have been shown to excrete 0.094 g/kg/d of urea nitrogen, accounting for 47% of dietary nitrogen.[39] Children or adults receiving a low but adequate protein intake excrete 40-45% of their dietary nitrogen as urea nitrogen. Thus, a child receiving 1.25 g/kg/day of protein has the obligatory requirement to synthesize 93 mg/kg/day of waste nitrogen as urea. This requirement can be met by patients with the neonatal form of CPS-I and OTC deficiencies if they receive 600 mg/kg/day of sodium phenylbutyrate which if completely conjugated with glutamine will lead to the excretion of 90 mg/kg/day of phenylacetylglutamine nitrogen.

[39] Waterlow The partition of nitrogen in the urine of malnourished Jamaican infants. Am J Clin Nutr 1963; 12: 235-40

These theoretical considerations were confirmed in an 8-year-old boy (of 27.2 kg body weight) with neonatal CPS-I.[40] When receiving 12 or 14 g/d of phenylbutyrate, 80-90% of the dose appeared in the urine as phenylacetylglutamine and phenylacetylglutamine nitrogen accounted for 42-44% of dietary nitrogen.

Evaluator's conclusions on dose finding for the pivotal studies

There were no dose finding studies submitted on which to base the clinical dosing regimen. The recommended dosing regimen is based upon theoretical considerations and reported clinical experience.

Efficacy

Studies providing efficacy data

All of the evaluable efficacy data is based upon the literature search.

No Pivotal Efficacy Studies were submitted as part of the application.

Other efficacy studies

- Lee 2010
- Lichter-Konecki 2011
- Kibleur 2014

Evaluator commentary: other efficacy studies

The available studies support that sodium phenylbutyrate treatment results in lower plasma ammonium, close to the normal range[37] is supportive of Pheburane being at least as effective as the Ammonaps. This is probably explained by improved compliance with treatment rather than the inherent efficacy of Pheburane.

Evaluator's conclusions on efficacy

The data on the clinical efficacy of Pheburane are limited. Most of the presented studies relate to the use of glycerol phenylbutyrate versus sodium phenylbutyrate in which glycerol phenylbutyrate does appear to have some minor advantage in nitrogen excretion.

There is evidence of good survival and perhaps prevention of hyperammonaemic episodes in patients treated with sodium phenylbutyrate. The study by Kibleur 2014 does suggest that Pheburane may be better tolerated than standard sodium phenylbutyrate and this may lead to better compliance with treatment.

- *The sponsor should better quantify the outcomes of treatment with sodium phenylbutyrate compared to historical controls in terms of:*
  - *Ammonia levels*
  - *Nitrogen excretion*

[40] Brusilow, S.W. (1991). Phenylacetylglutamine may replace urea as a vehicle for waste nitrogen excretion. Pediatric Research 29(2): 147-150.; Mistry, P.K. (2013). Rare disease clinical research network's urea cycle consortium delivers a successful clinical trial to improve alternate pathway therapy. Hepatology 57 (6): 2100-2.

- *Hyperammonaemic episodes*
- *Neurodevelopmental outcomes*

Safety

Studies providing safety data

There was no safety studies related directly to Pheburane submitted. There is only one submitted study (Bioequivalence Study LUC1001) including safety data on Pheburane. There are safety data related to Pheburane other formulations of sodium phenylbutyrate included in some of the published reports. In these reports, as they are uncontrolled for the use of sodium phenylbutyrate, it is not always possible to separate the effects of the underlying urea cycle defect from the effect from sodium phenylbutyrate or other therapies that the patients are receiving.
Finally, there is the first EU Periodic benefit-risk evaluation report (PBRER) Studies providing evaluable safety data from 31 July 2013 to 31 December 2015 which includes data from Study LUC1001 and published literature. There is overlap of patients between the reports and not all overlap is clearly identified in the published reports.

Pivotal studies that assessed safety as the sole primary outcome

No Pivotal Studies assessing safety were submitted as part of the application.

No Pivotal Efficacy Studies were submitted as part of the application.

Other studies

The overview of safety identifies adverse event reports in in the 3 comparative studies. The exposure of the patients to sodium phenylbutyrate is shown in Table 13 below).

Table 13: Adverse event reports for Sodium Phenylbutyrate from the comparator studies

Reference (No of pts)	*Duration NaPB pre-study mths*	*Dose NaPB Mean (SD) g*		*Reported AEs*
		Pre-study	*During study*	
Lee 2010 (n=14 adult)	97.89 (88.4)	13.49 (6.08)	12.22 (4.05)	Total of 21 AE in 7 out of 10 adult UCD patients during NaPB prescribed for average 9.04 years at average dose of 191 mg/Kg/d. Most AE categorized as mild (19/21). Six of 21 AE were treatment emergent AE in 5 patients -dyspepsia (1), gastro-esophageal reflux (1), increased appetite (1), dizziness (1), dysgeusia (1), and chills (1)
Lichter-Konecki 2011 (n=11 paed)	74.68 (48.2)	12.41 (4.39)	10.90 (3.858)	Possibly-related AEs were reported in 2 subjects on NaPB and 4 subjects on GPB. All were mild, except for one moderate AE of vomiting on GPB related to an intercurrent illness. No clinically significant laboratory or ECG changes were observed.
Smith 2013 (n=15 paed)	19.3 (17.2)	5.28 (2.45)	4.63 (2.16)	On Day 112 of 15 patients reported a total of 38 symptoms associated with NaPB or their UCD, the most common of which were body odour (6 patients), recurrent abdominal pain, vomiting after taking drug and refusal to eat due to smell or taste of the drug (3 patients each). Most symptoms either improved or resolved on Day 10. Improvement was reported for body odor and recurrent vomiting (5 patients each), vomiting after taking drug, abdominal pain, recurrent nausea and refusal to eat (3 patients each), and 1 patient each experienced improvement in the remaining symptoms. One patient who received NaPB through a G-tube and who received GPB orally reported a new onset of occasional vomiting upon or after taking GPB.

Patient exposure

The following table summarises the patient exposure to sodium phenylbutyrate in clinical trials.

Table 14: Exposure in clinical trials studying the use of sodium phenylbutyrate in the treatment of UCDs

Study	Condition	Sodium phenylbutyrate dose	Number of patients	Study Duration
		5.2g/d (SD)		
				years
(ATUc)	1LPI		18-64yrs: N=5	
Maestri (1995) Protocol IIb	24 ASD	250mg/kg/day	N=9 Neonates-infants (NOS)	Average treatment duration: 1.2 years
Maestri (1995)		450-600 mg/kg/day	N=19 Neonates-infants	Average treatment duration: 3.9 yrs

Study	Condition	Sodium phenylbutyrate dose	Number of patients	Study Duration
Maestri (1996) Protocol II	32 OTC	250-300 mg/kg/day	N= 22* All F Age range: 1-17 yrs	Treatment: 81 patient-years
Maestri (1996) Protocol III		450-600 mg/kg/day	N=28 All F Age range: 1-17 yrs	Treatment: 165 patient-years
Lee (2010)	8 OTC 1 ASS 1 HHH	191 mg/kg/day = 7.54 g/m^2	N=10 (4M; 6F) Age range: 21-73 yrs 38.2 (SD)	7-day open label, fixed sequence, sodium phenylbutyrate to GBP switchover. sodium phenylbutyrate average treatment duration :9.04 yrs (SD)
Lichter-Konecki (2011)	9 OTC 1 ASS deficiency 1 ASL deficiency	12.4 g/d (SD) (=322mg/kg/d or 10.2g/m^2)	N=11 (10F; 1M) Age: 10.2 (SD) Age range: 6-17 yrs	7-day open label, fixed sequence, sodium phenylbutyrate to GPB switchover (sodium phenylbutyrate average treatment duration: 74.68 mths (SD)
Diaz (2013)	40 OTC CPS1 ASS1	12.33g/d (SD)	N= 45 (14M; 31F) Age: 32 (SD)	14-day (sodium phenylbutyrate and GBP) randomized, double blind, double dummy crossover. sodium phenylbutyrate average treatment duration: 128.57mths(SD)
Smith (2013)	6 ASL 2 ASS 2 OTC	5.27g/d (SD)	N=15 (8M;7F) Age ranges: 2mths-5yrs; (29d-< 2yrs: N=4 2-<6 yrs N=11)	Open label, fixed sequence, sodium phenylbutyrate to GPB switchover ≤ 7 days. sodium phenylbutyrate average treatment duration: 19.3mths (SD)

*Use of NaPA or NaPB; unspecified number of each. Switch from phenylacetate to phenylbutyrate occurred when sodium phenylbutyrate was introduced in 1985

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

There are no data on the use of sodium phenylbutyrate in liver dysfunction. However, there are data to suggest that patients with cirrhosis have reduced capacity of the metabolic pathway of phenylacetate.

Renal function and renal toxicity

There are no systematic data presented on the risk of renal toxicity. The sponsor identified two cases of Fanconi syndrome with no further details supplied.

Electrocardiograph findings and cardiovascular safety

No significant ECG abnormalities were identified in the dossier. The only potential cardiovascular risk is related to the sodium load and fluid retention in patients with heart failure.

Postmarketing data

FDA Label

The dossier included the following extract from the FDA's approved drug information (label) for sodium phenylbutyrate (Buphenyl; FDA, 2009).

> **Adverse Reactions**
>
> The assessment of clinical adverse events came from 206 patients treated with sodium phenylbutyrate. Adverse events (both clinical and laboratory) were not collected systematically in these patients, but were obtained from patient-visit reports by the 65 coinvestigators. Causality of adverse effects is sometimes difficult to determine in this patient population because they may result from the underlying disease, the patient's restricted diet, intercurrent illness or sodium phenylbutyrate. Furthermore, the rates may be underestimated because they were reported primarily by the parent or guardian and not the patient.
>
> **Clinical Adverse Events**
>
> In female patients, the most common clinical adverse event reported was amenorrhea/menstrual dysfunction, which occurred in 23% of the menstruating patients.
>
> Decreased appetite occurred in 4% of all patients. Body odour (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of patients.
>
> Other adverse events reported in 2% or fewer patients were:
>
> Gastrointestinal: abdominal pain, gastritis, nausea and vomiting; constipation, rectal bleeding, peptic ulcer disease, and pancreatitis each occurred in one patient.
>
> Hematologic: aplastic anaemia and ecchymosis each occurred in one patient.
>
> Cardiovascular: arrhythmia and oedema each occurred in one patient.
>
> Renal: renal tubular acidosis
>
> Psychiatric: depression
>
> Skin: rash
>
> Miscellaneous: headache, syncope, and weight gain
>
> Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250–300 mg/kg/day for 14 days, repeated at 4-week intervals.

Manifestations were predominately somnolence, fatigue, and light-headedness; with less frequent headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy. These adverse events were mainly mild in severity. The acute onset and reversibility when the phenylacetate infusion was discontinued suggest a drug effect.

First EU Periodic benefit-risk evaluation report (PBRER)

This report included safety information collected for the medicinal product Pheburane (Sodium phenylbutyrate) covering the reporting period from date of authorisation 31 July 2013 to 31 December 2015. The report also included the French Compassionate Use Project (CUP) which was approved by the French Regulatory Agency in Sep 2012.

During the period under review, no actions have been taken or proposed by Lucane or any Competent Authority for safety reasons.

The report stated that Pheburane is authorised in 34 countries: all the EU countries as well as Norway, Iceland, Canada, Israel, South Korea and New-Zealand. Pheburane is marketed in 17 countries: France, United Kingdom, Spain, Germany, Netherlands, Belgium, Italy, Portugal, Greece, Sweden, Finland, Czech Republic, Canada, South Korea and distributed via compassionate use in Colombia and Turkey.

Exposure

The French Compassionate Use Project included 25 patients (see Table 15).

Table 15: French Compassionate Use Project enrolment (PBRER)

Age group	No of Persons
<20 years	21
21-30 y	2
31 – 40 y	1
>41 y	1

In the PBRER, the total exposure estimate is based upon supplied bottles of Pheburane.

In Europe this calculated at 71,039 daily doses (5.2 g/day).

The Outside of European exposure is a total of 36,640 daily doses (5.2 g/day) and 10,947 daily doses (12 g/day).

There were also 8 cases of off-label use in a range of other metabolic disorders; however, the sponsor states that no adverse events or any particular patterns of use have come to their attention which could be considered relevant for the interpretation of safety data.

Clinical trials

The PBRER reported that a single centre (Necker Hospital, France), pilot, open label, comparative, randomised, uncontrolled trial was initiated on February 2015 for 30 patients (2 groups of 15 patients) and was completed in September 2015. No serious AEs (SAEs) were observed during the trial. Two patients out of 13 at dose 15g/day who had to decrease to 7.5g/d for granularity issue with the product. The 13 (and 2 =15) patients at 7.5g/d had no treatment emergent AEs (TEAEs) reported.

New literature

The following papers were identified in an updated literature search:

- Burrage. L.C, Jain.M, Gandolfo.L, Lee. B.H, Members of the Urea Cycle Disorders Consortium, and Nagamani.S.C.S. Sodium Phenylbutyrate Decreases Plasma Branched-Chain Amino Acids in Patients with Urea Cycle Disorders. Mol Genet Metab. 113(0): 131–135. 2014
- Ucar.S.K , Kose.M, Altinok.Y.K, Canda.E, Kagnic.M, Duyu.M et.al. A MSUD Case: Sodium phenylbutyrate treatment during attack period. Springer. Page 239
- Schneider.B.L, and Vockley.J. Possible Phenylacetate Hepatotoxicity during 4-Phenylbutyrate Therapy of Byler Disease. J Pediatr Gastroenterol Nutr. Page 1-16. 2015.

This case was described as a case of hepatotoxicity received for sodium phenylbutyrate in an expanded access programme using a non-Marketing Authorisation Holder (MAH) marketed drug and the summary of the case is reproduced below:

> The case involved a 4-year-old boy diagnosed with Byler Disease (progressive familial intrahepatic cholestasis (PFIC)). The patient was started on Rifampin (rifampicin) on an unknown date. Liver biopsy at 44 months of age revealed Stage II/III fibrosis. Due to this (and following rejection of surgical intervention), Buphenyl (sodium phenylbutyrate) was prescribed at approximately 4 years and 6 months of age in a single patient expanded access compassionate (EAC) use. Buphenyl was discontinued after 6 months due to vomiting (due to poor palatability), although the patient was reported to have benefited from treatment. Following this, the patient was switched to an alternative EAC programme and administered glycerol phenylbutyrate. After 7 months on glycerol phenylbutyrate, Rifampin was discontinued to further assess the clinical response to glycerol phenylbutyrate. Thirty-five days after discontinuation of Rifampin, the patient was found to have significant hepatopathy and was admitted for supportive care. 24 h after his last dose of glycerol phenylbutyrate, serum phenyl acetate was 719 μM, while serum 4-phenylbutyrate was undetectable. Hepatitis screening done was negative (Hep E testing not performed). Over 2 weeks, liver disease returned to baseline. His jaundice worsened (total bilirubin 7.1 mg/dL) and his pruritus returned approximately 40 days after discontinuation of glycerol phenylbutyrate. Rifampin was restarted and his pruritus resolved. Liver biochemistries returned to baseline. At follow up, the child had no pruritus, had no features of advancing liver disease. The authors theorised that discontinuation of Rifampin therapy led to a reduction in CYP3A4 activity and a commensurate reduction in phenylacetate metabolism thereby leading to the toxic accumulation of phenylacetate.

There have been no other literature articles reporting the occurrence of hepatic toxicity following the use of sodium/glycerol phenylbutyrate.

The original articles were not supplied by the sponsor.

Signal and risk evaluation

The PBRER stated that no signals have been identified in the reporting period for Pheburane. In terms of a Risk Management Plan, The PBRER stated the following:

> There is no RMP in Europe for Pheburane. A Risk Management Plan (RMP) for Pheburane was submitted by Médunik to Health Canada. At the time of the MA, a number of minor deficiencies were identified. Overall, the RMP was considered to be acceptable. An updated version of the RMP was resubmitted in January 2016 and the review by Health Canada is on-going. The safety concerns summarised below are the risks consistent with the first version of the Canadian RMP which is the only one reviewed by their Authorities.

Evaluator's conclusions on safety

The dossier presents limited data on the safety of Pheburane in the treatment of patients with UCDs. Of the data presented, the first EU Periodic benefit-risk evaluation report is the most useful and highlights some potentially important signals including hepatotoxicity, blood dyscrasias and neurotoxicity.

The sponsor should address the following questions:

- *The sponsor should supply a complete summary of all of the Adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs.*
- *The sponsor should tabulate all adverse events attributable to sodium phenylbutyrate. This should include exposure data including dose, dose by size (weight and/or surface area) and length of treatment.*
- *The sponsor should tabulate all discontinuations due to adverse events attributable to sodium phenylbutyrate.*
- *The sponsor should submit a report on the single centre (Necker Hospital, France) pilot study of Pheburane, performed on 30 patients which was completed in Sep 2015*

First round benefit-risk assessment

Table 16: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Urea Cycle Defects (UCDs) are a collection of rare and potentially life-threatening metabolic disorders with raised ammonia as a common pathway in the disease process. *Pheburane offers a palatable form of sodium phenylbutyrate treatment as an alternative nitrogen excretor. It should be noted that phenylbutyrate is a standard component of the current protocols for treating UCDs*	*The strength of the application is the fact there is not a formulation of phenylbutyrate registered for use in Australia. Of the available formulations, Pheburane appears to offer significant advantages over other formulations of sodium phenylbutyrate but appears to be bioequivalent.* *There is significant uncertainty about both the actual efficacy and safety that Pheburane offers. Because the innovator product is not marketed in Australia, the regulatory authority (TGA) does not have access to the full original dossier on which sodium phenylbutyrate was approved in other countries. Because of this, the evaluation is based upon incomplete literature based data on which to assess both the efficacy and safety.*

Table 17: First round assessment of risks

Risks	Strengths and Uncertainties
The main risks are related to the lack of data and the poor quality of the available data as it is presented. Specifically, efficacy cannot be assured and the safety data are incomplete. There is also uncertainty around dosing as no dose efficacy data are available in the treatment	*The available data is presented in a suboptimal format to clarify the risks around efficacy and safety. A reanalysis of the available literature in tabular form may clarify the efficacy and safety data. This is important as it is unlikely that any further data from the literature will be*

Risks	Strengths and Uncertainties
of UCDs. However, data are available in other disease states (mostly cancer) identifying dose-limiting toxicity.	*forthcoming to change the risk assessment.* *Reassuringly, the first European PBRER stated that no signals have been identified in the reporting period for Pheburane.*

First round assessment of benefit-risk balance

Pheburane (sodium phenylbutyrate) is a novel treatment for the hyperammonaemia associated with UCDs which are collection of rare and severe inborn errors of metabolism. There are no similar treatments registered for use in patients with UCDs in Australia and the registration of Pheburane would be a significant therapeutic advance for Australian patients. However, the dossier is based upon a single bioequivalence study comparing Pheburane to Ammonaps (the innovator product registered overseas but not registered in Australia). The sponsor has supplemented their application with literature about sodium phenylbutyrate, but this literature lacks the level of pharmacokinetic, efficacy and safety data which are usual in an application of this type. There are also significant deficiencies in the analysis and presentation of the available data. If the deficiencies in the submission can be addressed, the benefit-risk balance would favour registration of Pheburane with careful post-approval surveillance for adverse events.

First round recommendation regarding authorisation

The evaluator does not currently recommend authorisation of Pheburane until the deficiencies in the data are addressed. However, with clarification of the questions about pharmacokinetics, efficacy and safety adequately addressed authorisation could be recommended.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Pheburane, in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Pheburane are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of Pheburane, given the proposed usage, is favourable.

Given the nature of the urea cycle disorders, the potential adverse neurological outcomes from untreated disease, and the limited available treatment. The available efficacy and safety data, albeit limited, supports the relative safety of Pheburane when compared to the poor neurological outcomes described for untreated urea cycle disorders. Pharmacokinetic data supporting the proposed dosing regimen is inadequate but could be improved through post-marketing pharmacokinetic studies.

Second round recommendation regarding authorisation

Approval of Pheburane is recommended as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.

The evaluator did not recommend authorisation of Pheburane in the first-round assessment until the deficiencies in the data were addressed. It is clear from the responses of the sponsor, that they have a limited ability to address these concerns as the application, other than a single bioequivalence study and the available literature. Given the nature of the UCDs, the potential adverse neurological outcomes from untreated disease and the limited available treatments, the evaluator concludes that the authorisation could be recommended.

The sponsor should be encouraged to collect detailed ongoing safety and efficacy data as part of therapy. Furthermore, the sponsor should conduct a post-marketing pharmacokinetic study using a sparse-sampling technique to better characterise the dose-concentration relationship over the proposed dosing range in order to better justify the current dosing regimen.

VI. Pharmacovigilance findings

Risk management plan

- The sponsor has submitted Australian RMP version 1 dated 28 January 2016 in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (Table 18).

Table 18: Summary of ongoing safety concerns

R=routine and A=additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Risk of metabolic acidosis	ü	–	ü	–
	Risk of blood dyscrasias	ü	–	ü	–
	Risk of clinical lab abnormalities (changes in blood proteins, electrolytes,	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	enzymes and hepatic enzymes)				
	Risk of neurotoxicity	ü	–	ü	–
Important potential risks	Risk of medications errors	ü	–	ü	–
	Risk of drug interactions (probenecid, haloperidol, valproate, corticosteroids)	ü	–	ü	–
	Hyperbilirubinemia in neonates	ü	–	ü	–
	Risk of reproductive toxicity	ü	–	ü	–
Missing information	Risk of hepatic toxicity	ü	–	ü	–
	Use in patients with renal insufficiency	ü	–	ü	–
	Off-label use	ü	–	ü	–
	Use in patients with congestive heart failure/conditions of sodium retention with oedema	ü	–	ü	–
	Use in patients with DM/patients with sugar intolerance or malabsorption or sugar enzyme insufficiency	ü	–	ü	–
	Use in pregnancy	ü	–	ü	–
	Use during breastfeeding	ü	–	ü	–
	Use in elderly patients	ü	–	ü	–
	Risk of carcinogenicity	ü	–	ü	–

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Highlighted safety concerns were added in response to the first round evaluation reports.

- The sponsor submitted the revised AUS-RMP version 3 dated 17 January 2017 in response to the second round RMP evaluation report.
- The clinical evaluator raised issues regarding the adequacy of the draft Consumer Medicine Information (CMI) in the second round clinical evaluation report. Further recommendations have been made by the RMP evaluator to improve the safe use of the product by consumers.

New recommendation - Post second round

The sponsor has adequately addressed the recommendations made in the first round RMP evaluation, except Recommendation 3. Recommendation 9 (made in the second round evaluation) also remains outstanding.

Recommendation 3:

The sponsor has stated that hepatotoxicity has been added as an important potential risk. The evaluator has noted that in the updated AUS-RMP, hepatotoxicity has been added under SVII.1 'Newly identified safety concerns' but not to Part II; Module SVIII - 'Summary of safety concerns'. Given that the patient in the only case report already had progressive familial intrahepatic cholestasis and had received rifampicin treatment, the case is more relevant to 'use in patients with hepatic insufficiency'. The evaluator has noted that in Table 25 under section VI.1.1, 'use in patients with hepatic insufficiency' is classified as an important potential risk which differs from Table 21 under Module SVIII in which 'use in patients with hepatic insufficiency' is missing information. The sponsor should ensure that all sections of the RMP are updated, and also correct the terminology used to 'hepatotoxicity'.

Recommendation 9:

There is significant inconsistency in the Summary of Safety Concerns (Part II: Module SVIII) and that in the Summary of the Risk Management Plan by Product (Part VI.1.1). The RMP should be an internally consistent document and the sponsor is required to submit a revised version which addresses these discrepancies

The following new recommendations are made to incorporate advice made in the second round clinical evaluation report:

Recommendation 10:

The diagram of the dosing devise should to corrected (flipped horizontally) to clearly display the numbers (similar to the image in the New Zealand CMI). Both images on page 2 [not in this AusPAR] should also be of improved graphical quality

Recommendation 11:

Information should be provided to the patient in the CMI to clarify the units. That is, a statement that 1,5 is equivalent to 1.5 or similar.

Recommendation 12:

The following advice should be added to the PI and CMI in bolded text: 'the calibrated measuring spoon is for measuring Pheburane only and must not be used to measure other medications';

Recommendation 13:

The CMI should be included as a package insert to ensure patients are provided with sufficient information to ensure accurate dosing.

RMP wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement the AUS-RMP version 3 dated 17 January 2017 and any future updates as agreed with the TGA.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator had no objection to the approval of Pheburane (sodium phenylbutyrate) on chemistry and quality control grounds. The following was noted during the evaluation of the quality aspects of this submission for Pheburane granules:

- PBA, 4-phenylbutyric acid is an aromatic short-chain fatty acid that is a chemical derivative of butyric acid, naturally produced by colonic bacteria fermentation. It is a pro-drug that is rapidly metabolised to PAA.
- The API is a hygroscopic, white or yellowish white powder freely soluble in water and in methanol, practically insoluble in methylene chloride.
- The partition coefficient of 2.42 with a dissociation constant pKa of 4.76 (phenylbutyric acid)
- The pH of a solution in water is 6.5 – 7.5.
- The drug substance specification is according to the Ph.Eur. monograph and includes tests and limits for 3-benyloylproprionic acid and alfa tetralone. Impurities and residual solvents identified were satisfactorily controlled.
- Pheburane contains sodium phenylbutyrate as 483 mg/g of granules in a pack size of 174 g, presented in HDPE bottles with desiccant PP cap in a child resistant container.
- The drug product is white to off-white granules manufactured by standard process with active ingredient spray coating on sugar pellets that are the Pheburane granules. The granulate particle size is controlled.
- The formulation contains ethyl cellulose, hydroxypropyl methyl cellulose, macrogol, maize starch, povidone and sucrose as excipients to mask the taste of the active ingredient.
- The calibrated measuring spoon dispenses up to 3g of sodium phenylbutyrate in graduations of 250 mg.
- The stability data supported a shelf-life of 36 months when stored below 30°C protected from light in the proposed packaging.

Nonclinical

The nonclinical evaluator noted significant deficiencies in the quality and quantity of nonclinical data to support the application, however considered this may be acceptable for a substance that has had extensive clinical use and is intended for a life threatening condition.

The nonclinical evaluator noted the following:

- The sponsor provided EMA evaluation reports for Ammonaps and Pheburane and FDA and EMA reports for Ravicti (glycerol phenylbutyrate, GPB) but noted that none of the GPB data were available and the data that was presented had a number of deficiencies and limitations.
- No nonclinical pharmacokinetic or safety pharmacology studies were conducted with Pheburane. Nonclinical safety presented for GPB was taken into consideration given that the phenylbutyric acid molecules on the glycerol backbone in GPB are expected to be transformed in an identical manner to sodium phenylbutyrate, making the GPB nonclinical studies of relevance for the submission.
- GPB in monkeys had a similar pharmacokinetic profile to humans and had wide tissue distribution after oral administration. There was significant CNS exposure to PBA and PAA after IV administration of sodium phenylbutyrate in monkeys.
- GPB exposure in cynomolgus monkey produced CNS adverse events. Inhibition of hERG channels occurred at PBA and PAA concentrations 560 fold and 56 fold, respectively the unbound adult UCD concentrations in adults. QTc prolongation was seen with oral GPB doses of 4 g/kg however the clinical relevance of this finding for the proposed dosing is unknown.
- Plasma-protein binding of PAA and PBA was concentration dependent in animals (81 to 98%) and humans (37 to 66%) but binding for PAGN was not concentration dependent (1.3 to 12%)
- PBA undergoes beta-oxidation in the liver and most other organs to PAA, which may be hydrolysed via esterases in the liver and blood. In humans and higher primates PAA is predominantly conjugated to PAGN. Excretion is predominantly renal in animals and humans.
- PAA inhibition of human hepatic CYP1A2, CYP2C8 and CYP2C9 in vitro is of possible clinical relevance. Both PBA and PAA showed minimal potential for induction of human hepatic CYP1A2 and CYP3A4/5. PAA is actively secreted by probenacid-sensitive renal organic anion transporters. No formal investigations of potential pharmacokinetic interactions have been conducted.
- There were no repeat-dose toxicity studies for sodium phenylbutyrate.
- Carcinogenicity tests have not been conducted with sodium phenylbutyrate. GPB rat study showed an increased incidence of pancreatic tumours at 650 mg/kg/day in males and 900 mg/kg/day in females. At 900 mg/kg/day female rats had an increased incidence of thyroid, adrenal and uterine tumours.
- Sodium phenylbutyrate was not genotoxic in Ames test although the evaluator noted it was underpowered to detect A-T and G-C base pair mutations. An in vitro chromosomal aberration assay in human lymphocytes and an in vivo micronucleus assay in rats PAA and PAGN were not genotoxic the Ames test or an in vitro chromosomal aberration assay in CHO cells. Overall the evaluator was satisfied, based on the data of adequate quality, sodium phenylbutyrate is not genotoxic.
- Developmental toxicity was inadequately investigated. In a rat model of maternal phenylketonuria PAA was neurotoxic. Exposure to PAA in pregnancy or early post-

natal life was associated with reduced fetal brain weight, cognitive impairment and neuroanatomical defects. From GPB animal reproductive toxicity studies doses of up to 350 mg/kg/day in rabbits and 300 mg/kg/day in rats had no effect on embryofetal development however doses ≥ 650 mg/kg/day produced maternal toxicity, reduced fetal weight, skeletal variation and a wide range of non-specific malformations. Conversely, pups of pregnant rats exposed to doses up to 900 mg/kg/day up to 92 days post-partum did not show developmental effects on growth or cognition.

- Based on the information presented a Pregnancy category of B3 was recommended. The sponsor proposes to contraindicate Pheburane in pregnant women and in breast feeding
- A juvenile toxicity study in neonatal rats treated orally with GPB found comparable toxicities to adults following oral administration of doses up to 1.2 g/kg/day for 7 weeks.

Clinical

The clinical evaluator recommended rejection at the first round but following the evaluation of the responses to the clinical questions the clinical evaluator recommended approval for the sponsor's requested indication.

The clinical dossier for this mixed submission comprised:

- One bioequivalence study comparing Pheburane and Ammonaps (the EU registered sodium phenylbutyrate granules)
- 14 literature based study reports relating to pharmacokinetics, efficacy and safety
- The first EU periodic benefit-risk evaluation report dated 2016.

The evaluator noted the submission was not well integrated and had content deficiencies, some of which were addressed in the responses to questions.

Clinical study

The main purpose of this study was to allow linkage of the sodium phenylbutyrate used in literature with Pheburane.

Study LUC1001 was a randomised, fasting, two sequence, parallel group study in 13 adult healthy volunteers (5 male and 8 female) aged 19 to 50 years to test the bioequivalence of Ammonaps with Pheburane. Doses of 2.5 g and 5 g were tested. After a single 2.5 g dose C_{max} of about 1 mmol/L was reached after 1 hour, and the elimination half-life was estimated to be 0.8 hour. Measurable plasma levels of PAA and PAGN were detected 30 to 60 min after oral dosing (C_{max} 45.3 and 62.8 microgram/mL, respectively). After 5 g PBA dose T_{max} for both metabolites increased to about 3.5 hours. Elimination half-lives were estimated at 1.3 and 2.4 h for 2.5 g and 5 g doses respectively.

The point estimates of the ratios of test (Pheburane) and reference (Ammonaps) for the 5 g dose for C_{max} 94.32% (94.12% CI: 86.95 – 102.31), $AUC_{0-\theta}$ 95.61% (94.12% CI: 90.34 – 101.19), and $AUC_{0-\infty}$ 95.80% (94.12% CI: 90.80 – 101.08) demonstrated bioequivalence of the two formulations within standard bioequivalence limits. The difference between T_{max} for sodium phenylbutyrate of 0.75 h and 0.5 h for Ammonaps was not statistically significant

Literature supporting the submission

The sponsor listed the following studies as the studies for evaluation to support the submission. Although not presented in this manner in the submission, the studies can be

grouped according to those comparing GPB with sodium phenylbutyrate, studies reporting the use of Pheburane and other literature. In addition, the sponsor has referred to other studies for safety and pharmacology information as referenced in the clinical evaluation report.

Studies reporting the use of pheburane

Kibleur et al 2014[37] was a study conducted in the French Autorisation Temporaire d'utilisation cohorte prgramme to analyse the safety and efficacy of Pheburane in UCD. The cohort was established in 2012 and data collection terminated approximately 1 year later after Market Authorisation was granted in Europe. The protocol allowed collection of demographics, dosing characteristics, concomitant medications, adverse events and clinical outcome during the period of treatment. Patients included in the study ranged in age from 3 years to 64 years and included 16 female patients, 8 male patients and one with gender unspecified. All were treated with Pheburane and 60% had concomitant sodium benzoate.

Studies comparing GPB with sodium phenylbutyrate

Lee et al 2010 was a Phase II, prospective open-label, fixed sequence, switch-over study conducted in 10 adults (4 male, 6 female) with a mean age of 38.2 years with UCD taking maintenance sodium phenylbutyrate, comparing GPB to sodium phenylbutyrate. Blood ammonia, blood and urine metabolites were compared after 7 days of three times daily dosing on either drug (both dosed to deliver the same amount of PAA).

Berry et al 2014 The paper reported the outcomes for 26 patients with a mean age of 7.1 years from two Phase II open-label cross-over studies that compared 24 h ammonia exposure, and glutamine levels with equivalent dosing of GPB and sodium phenylbutyrate. These patients plus an additional 23 patients then received GPB in one of 3 open-label extension studies that assessed long term ammonia control, number of hyperammonaemic crises, amino acid levels and patient growth.

Smith et al 2013 this was an open-label cross-over study comparing the ammonia levels, PK and safety of glycerol phenylbutyrate and sodium phenylbutyrate in 15 children aged < 6 years with confirmed or clinically suspected UCD, receiving sodium phenylbutyrate for at least 5 days. Four children were aged 29 days to < 2 years, and the remainder were 2 to < 6 years of age. Prior to entering the study 10/15 patients had at least 1 hyperammonaemia episodes, with some patients having 7 episodes. After a 10 day cross-over period patients continued on GPB were followed for up to 12 months.

Lichter-Konecki et al 2011 was a Phase II open-label fixed sequence cross-over study in 11 children (9 OTC, 1 ASS, 1 ASL) aged ≥ 6years (mean age 10.2 years) being treated with sodium phenylbutyrate for a UCD for an average (SD) of 74.7 (48.2) months at an average dose of 322 mg/kg/day or 10.2 g/m^2 . After at least 7 days of sodium phenylbutyrate dosed three times daily at doses prescribed by the investigator patient underwent PK and ammonia level measurement. Patients were switched to a PBA molar equivalent dosing of GPB and retested after 7 days.

Diaz et al 2013 reported the results of a pivotal Phase III randomised, double-blind, cross-over trial comparing ammonia control and PK, and combined the results of 4 studies involving long and short term GPB treatment of UCD patients aged >= 6 years, including studies reported in the publications by Lee et al 2010 and Lichter-Konecki et al 2011 included in this submission.

Mokhatarni et al 2012 was population PK study utilising PK data from 3 cross-over studies of sodium phenylbutyrate and GPB from 54 adults and 11 children.

Monteleone et al 2012 was a population PK study using data from 64 patients, 53 adult and 11 children from Phase II and III cross-over comparisons of the PK of sodium phenylbutyrate and GPB.

Nagamani et al 2015 collected data on GPB treatment-associated symptoms from 100 patients/carers with confirmed or suspected UCD receiving a stable dose of sodium phenylbutyrate who were switched to GPB. The survey was conducted using a non-validated UCD-specific questionnaire using a pre-defined list of symptoms associated with these medications. Responses were collected at baseline (on sodium phenylbutyrate) and after 3 months on GPB. Patient ages ranged from 2 months to 60 years.

Other literature

Maestri 1991, 1995, 1996 describe a Phase III study conducted in the US and Canada over a 10 year period.

Maestri 1991 followed 43 fetuses at risk of UCD based a UCD diagnosis in a sibling. Prospective protocols to prevent hyperammonaemia were implemented within 2 h of birth and 12 hourly urea, ammonia and amino acids were measured in cord blood and plasma for 72 h, and the infants were treated and followed over 10 years. The nitrogen scavengers in the initial protocols did not include sodium phenylbutyrate; however sodium phenylbutyrate was introduced into the protocol when it became available in 1987. Long-term metabolic control, clinical control (number and duration of hyperammonaemic episodes and peak plasma ammonia), and developmental progress and intelligence after 6 months of age were measured.

Maestri 1992 was a case report of a child with OTC deficiency treated with a low protein diet, citrulline and sodium phenylbutyrate 500 to 600 mg/kg/day.

Maestri 1995 monitored the long term survival of patients with neonatal onset ASD treated with pre-specified protocols to provide alternative pathways of waste nitrogen excretion. The protocols of relevance were IIb 250 mg/kg/day sodium phenylbutyrate (9 neonates and infants) for an average duration of 1.2 years and protocol IIIb (19 neonates and infants) 450 – 600 mg/kg/day for an average duration of 3.9 years.

Maestri 1996 described the long term outcomes of girls taking sodium phenylbutyrate for UCD according to pre-specified protocols. The protocols of relevance were II (22 girls, 250 – 300 mg/kg/day sodium phenylbutyrate) and III (28 girls, 450 – 600 mg/kg/day sodium phenylbutyrate).

Pharmacology

The sponsor provided literature to describe the pharmacology of sodium phenylbutyrate:

Pharmacokinetics

The pharmacology of sodium phenylbutyrate was discussed by the quality evaluator based on material in the quality sections of the submission:

- Formal ADME (absorption/distribution/metabolism/excretion) studies were not included in the submission for Pheburane and the pharmacology information was derived from literature
- Sodium phenylbutyrate is rapidly absorbed under fasting conditions t max 1 h after a single oral dose of 5 g, plasma levels detectable in 15 minutes, C_{max} 195 µg /mL. The site of absorption is not addressed but is most likely to be the small intestine.
- Intravenous PBA PK of doses between 150 mg/kg and 500 mg/kg associated with initial plasma concentration ranging between 300 and 2000 µmol/L rising to a plateau within 4 to 6 h of infusion.
- Formal distribution data were not presented however the Vd was reported as 0.2 L/kg

- Phenylbutyrate is rapidly converted via beta-oxidation by medium chain acyl-CoA dehydrogenase to its active metabolite PAA, then conjugated to form PAGN, that mediates waste nitrogen removal through urinary excretion
- Measurable levels of PAA and PAGN were detected 30 to 60 minutes after oral dosing. The mean times to peak concentration of these metabolites were 3.55 h and 3.23 h respectively.
- The formation of PAGN from PAA is saturable, although accumulation of PAA acid is not appreciable among any age groups, and at very high doses (500 mg/kg/day or 2g/m2) there appears to be saturable metabolism of PBA to PAA. Exposure to PAGN was independent of PBA dose.
- The elimination half-lives of PAA and PAGN were 1.3 to 2.4 h respectively. In most patients with UCD or haemoglobinopathies receiving doses of 300 to 650 mg/kg/day up to 20 g/day) no plasma level of PAA could be detected after overnight fasting.
- 80 to 100% is excreted by the kidneys within 24 h as PAGN.
- The PK of PBA has not been studied in patients with renal impairment
- In male patients with hepatic cirrhosis administered 3 doses of 20 g orally daily PBA plasma concentrations were similar to healthy subjects and UCD patients but conversion to PAGN was slower and both PBA and PAA were detected in the urine.
- In women, AUC and C_{max}, with a 30 to 50% increase in sodium phenylbutyrate and PAA levels but not PAGN possibly due to the lipophilicity of sodium phenylbutyrate
- There are no dedicated PK studies in the paediatric population with UCD for Pheburane. In young children[41] AUC and C_{max} in the GPB comparison PK studies were slightly lower than in adult studies, and PAA was slightly higher, whereas PAGN was comparable. However the percentage of orally administered sodium phenylbutyrate excreted as PAGN was similar to the adult studies.
- There were no PK data in the elderly.
- Population PK demonstrated high inter- and intra-individual variability in plasma metabolite levels. Intersubject variability was explained by a wide range of doses the study population received and differences in their first pass metabolism and the intra-subject variability was explained by the short metabolite half-life and limits the utility of random measurement of plasma metabolite. Morning spot urine PAGN and 24 hour urinary PAGN correlated strongly with dose and appeared to be clinically useful non-invasive biomarkers for compliance and therapeutic monitoring.
- Population PK model that best fit the data was characterised by partial conversion of PBA to PAGN prior to reaching the systemic circulation, saturable conversion of PAA to PAGN (Km approximately 161 microgram/mL).Metabolic clearance was proportional to body surface area (BSA). Fractional presystemic metabolism was higher for children than adults with sodium phenylbutyrate (23% versus 43%, respectively). Differences in the proportion of PBA metabolised pre-systemically appear to account for the drug-related differences in PAA levels, even with dosing at the upper end of the proposed range where PAA exposure show greatest variability the upper 95%ile for the C_{max} of PAA was < 500 microgram/mL.
- PAA to PAGN conversion is saturable and the higher PAA levels in paediatric patient as compared with adult UCD patients reflects BSA related changes in PAA clearance and higher per weight dosing in children.

[41] Lichter-Konecki U, et al Ammonia control in children with urea cycle disorders (UCDs); Phase II comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Genet Metab. 2011; 103

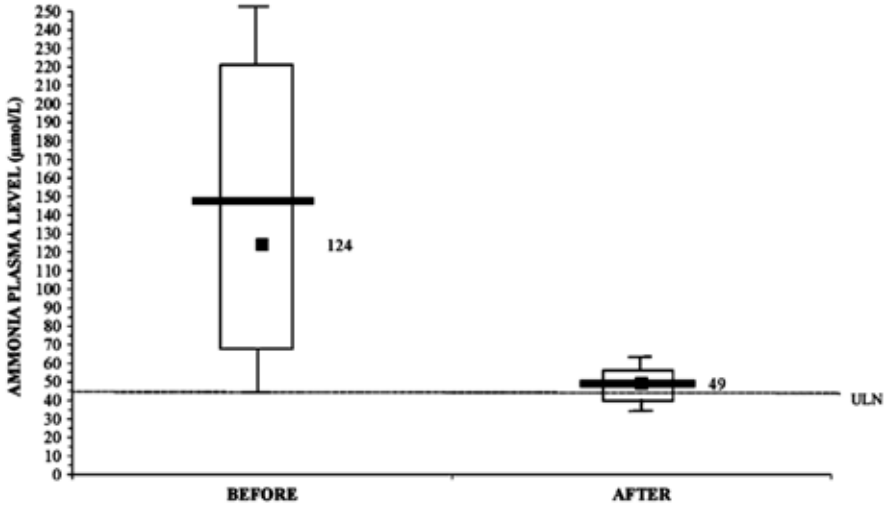
- There were no formal food interaction studies. Administration with food is based on clinical practice.
- The clearance of PBA was higher, as was a higher conversion to phenylacetate in a PK study of CNS malignancies and anticonvulsants than in a previous study of non-CNS malignancies without anticonvulsants suggesting an interaction. Although not detected in the non-clinical testing, Schneider 2015[42] hypothesised CYP3A4 may be important for PAA metabolism.
- No dose finding studies were provided upon which to base the dosage regimen. The doses appear to be derived from first principles: a calculated nitrogen load, and the dose to allow excretion of about 47% of dietary nitrogen. The theoretical considerations were confirmed in an 8 year old boy who weighed 27.2 kg with neonatal CPS-I.[40] He received 12 or 14 g/day of phenylbutyrate, 80 to 90% of the dose appeared in the urine as PAGN and PAGN nitrogen accounted for 42 to 44% of dietary nitrogen.

Pharmacodynamics:

Ammonia levels and glutamine levels were reported as outcome measures in a number of studies.

- Mean plasma ammonia in the 6 months prior to inclusion was 124 µmol/L and in the period after treatment was 49 µmol/L (upper limit of normal (ULN) 45 µmol/L) in 25 patients treated with Pheburane. Plasma ammonia levels were below the ULN for 47% of the treated patients, and only 6% were >2 times ULN (Kibleur 2014[37], see Figure 7).

Figure 7: Box and whisker plats of maximum plasma ammonia values in the 6 months before include in the cohort ATU and then under Pheburane (Kibleur 2014)



- Smith et al 2013[43] found blood ammonia levels were elevated in 7/15 patients at the beginning of the study, in 4/14 patients at 8 hours, 6/14 patients at 12 h and 5/15 patients at 24 hours. The mean C_{max} of ammonia was 53 µmol/L and the mean (SD) AUC was 914 (630.206) µmol/L*h. While numerically greater than for GPB, the

[42] Lichter-Konecki U, et al Ammonia control in children with urea cycle disorders (UCDs); Phase II comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Genet Metab. 2011; 103

[43] Smith W et al, Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Journal of Pediatrics. 162(6):1228-34, 1234.e1, 2013.

differences were not statistically significantly different. Mean systemic exposures to PBA, PAA and PAGN were similar.

- Lee 2010[44] showed individual ammonia varied up to 7 fold in a 24 hour period. PAGN of 10 g per day suggested optimal control. This equated to a daily dose of about 12 g sodium phenylbutyrate. Time normalised ammonia values for GPB were about 30% lower than sodium phenylbutyrate. Blood ammonia and UPAGN correlated strongly and inversely ($r = -0.82$, $p<0.0001$).
- Plasma glutamine and ammonia concentrations are correlated ($r=0.77$) for values across the range but the correlation was poor for values < 30 µmol/L. When plasma glutamine was below 800 µmol/L ammonia levels were normal however for levels above 1000µmol/L 86% were associated with elevated levels.[45] In the surviving ASS patients in Maestri 1995[46], plasma glutamine was 688 µmol/L and 95% of values were below 1080 µmol/L on treatment including sodium phenylbutyrate.
- The improved nitrogen excretion does not appear to be at the expense of muscle tissue.

Efficacy

The data on the clinical efficacy of Pheburane are limited and no particular study was considered pivotal to the submission by the evaluator.

Historical data

One year survival was 14% in a study of 28 patients (5 CPS-1, 10 OTC, 6ASS, 7ASL) and 3 of the 4 survivors were mentally disabled. After the implementation of a waste nitrogen strategy (not sodium phenylbutyrate) a 92% one year survival was reported for 26 children with complete UCD and neonatal hyperammonaemia coma (3 CPS-1, 7 OTC, 8ASS, 8ASL).There were 4 subsequent deaths, including 2 from hyperammonaemia. Msall 1984[47] reported the neurological outcomes for 24 children with UCD. Of the 24 that survived the first year 19 had one or more developmental disabilities. Normal function was found in 21%, cerebral palsy in 46%, mental retardation in 79%, seizure disorder in 17%, blindness in 4%, microcephaly in 54% and multiple disabilities in 46%. No correlation was found between peak ammonia levels (351 to 1800µmol/L) and intelligence quotient (IQ) score at 1 year but there was a good correlation with the length of time of hyperammonaemic coma and normal IQ was associated with coma lasting < 3 days.

Hyperammonaemia:

The risk of seizures and episodes of decreased consciousness are increased with acute and chronic hyperammonaemia. Kibleur et al 2014[37] noted 10 patients, ages 3 years to 64 years with 1 to 3 episodes of hyperammonaemia in the 6 months before Pheburane treatment had no episodes in the 3 to 11 months of the study.

The long term study reported by Maestri and by Feillet 1998[48] included 128 patients treated with nitrogen scavengers for 5 to 15 years. The annual incidence of

[44] Lee B, Rhead W, Diaz GA, Scharschmidt BF, et al.: Phase II comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. Mol Genet Metab 2010; 100(3): 221-8

[45] Maestri NE, McGowan KD and Brusilow SW: Plasma glutamine concentration: a guide in the management of urea cycle disorders; J Pediatr 1992; 121 (2): 259-61

[46] Maestri NE; Clissold DB; Brusilow SW. Long-term survival of patients with argininosuccinate synthetase deficiency. Journal of Pediatrics. 1995; 127(6):929-35

[47] Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED (1984) Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. N Engl J Med 310:1500–1505

[48] Feillet F, Leonard JV. Alternative pathway therapy for urea cycle disorders. J Inherit Metab Dis 1998;21 Suppl 1:101-11.

hyperammonaemic episodes ranged from 0.4/patient year in the female OTC group treated with 250 mg/kg/day sodium benzoate and 250 to 300 mg/kg/day sodium PAA or sodium phenylbutyrate to 1.4/patient year in the ASS treated in the earliest protocol in 1980 with sodium benzoate alone, with frequency of 0.9 episodes/patient year across the whole study.

In girls with OTC the frequency of hyperammonaemic episodes decreased with increasing patient age from 1.0 episode per patient year aged < 5 years to 0.1 episode per patient year by age ≥ 20 years, and with the use of PAA or sodium phenylbutyrate.[49]

Cognitive development

Msall showed developmental outcome in UCD patients is related to the duration of Grade 3 or 4 coma. In Maestri 1991[50], 9/12 patients presented with some developmental delay, mostly in language. Among the 24 ASS patients reported in Maestri 1995[46], 15 survived the first year; 12 had neonatal ammonia of 400 to 2000 µmol/L and grade 3 to 4 coma for 24 to 168 hours, and 11 of those had an IQ <55 at 8 years and the remaining 4 although had initially higher scores at assessment end had IQs in the range of 50 to 70.

Among the cohort of 28 patients with late OTC presentation, 12 had an IQ >85 (5 were treated prospectively with waste nitrogen excretion stimulation) and 16 had a disability. Nineteen of the 23 patients with longitudinal testing had a stable IQ and the remainder had a reduction of more than 15 points.

Growth

Mean height and weight z-scores were within normal range at baseline were not significantly different from normal after 12 months treatment with GPB.[51] In Maestri et al 1995[46] all patients showed growth retardation but most had height for weight z-scores within 2 SD of the mean. Girls with OTC maintained appropriate weight for height.[49]

Survival

Maestri et al 1995 reported a cumulative survival of 87.5% at 5 years and 72% at 10 years in 24 neonatal-onset ASD patients born before 1990 and rescued from hyperammonaemic coma. In 32 girls with OTC reported by Maestri in 1996[49], survival was 90.6% at 5 years.

Safety

The safety data were primarily derived from publications and were therefore limited. The safety set included 153 patients: 106 OTC, 9 ASS, 3 CPS, 8 ASL, 24 ASD 2 HHH and 1 LPI.

Exposure ranged from 19.3 months to 165 patient years. The sponsor presented the following table of adverse events from clinical trials in the submission.

[49] Maestri NE et al, Long-term treatment of girls with ornithine transcarbamylase deficiency. New England journal of medicine 1996 VL: 335 NO: 12 PG: 855-9

[50] Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr. 1991 Dec;119(6):923-8.

[51] Berry SA; Lichter-Konecki U; Diaz GA; McCandless SE; et al. Glycerol phenylbutyrate treatment in children with urea cycle disorders: pooled analysis of short and long-term ammonia control and outcomes. Molecular Genetics & Metabolism. 112(1):17-24, 2014.

Table 19: Sponsor's overview of adverse events reported for sodium phenylbutyrate in studies of patients with urea cycle disorders

Study	Sodium phenylbutyrate dose	Number of patients	AEs reported (n or % of n)
Weich (1997)	NR	12 (4M; 8F)	Menstrual Disturbances (23%) Anorexia Biochemical abnormalities
Feillet (1998)	NR	6 (5M; 1F)	Oral mucositis Fanconi syndrome (2)
Lee (2010)	191 mg/Kg/d equivalent to 7.54 g/m2 for an average of 9.04 years	6	Dyspepsia (1) gastro-oesophageal reflux (1) increased appetite (1) dizziness (1) dysgeusia (1) chills (1).
McGuire (2010)		10	dizziness (5) headache (4) nausea (3)
Lichter-Konecki (2011)	mean dose = 12.4 g/d or 322 mg/Kg/d; range =198 – 476 mg/Kg/d)	28 (22M; 6F)	lymphadenopathy (1) decreased appetite (1) cardiac murmur (1)
Diaz (2013)	(12.33 g/d) for an average of 128.57 months	45 UCD (40 OTC, 2 CPS-I, 3 ASS) patients; 51% reported AE	Diarrhea Flatulence abdominal discomfort dyspepsia nausea vomiting oral discomfort.
Pheburane versus Ammonaps Bioequivalenc estudy		12	headache (15) ageusia (5) weakness (1) Vomiting (1)

Study	Sodium phenylbutyrate dose	Number of patients	AEs reported (n or % of n)
ATUc (Autorisation Temporaire d'utilisation cohorte)			No AEs reported

The sponsor has proposed the following account of adverse events for the PI. Frequencies used are the CIOMS frequencies. Given the small numbers of patients in the safety set any event reported more than once would be considered common.

Table 20: Sponsor's overall summary of adverse events for sodium phenylbutyrate as proposed for the PI.

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anaemia, ecchymosis
Metabolism and nutrition disorders	Common	metabolic acidosis, alkalosis, decreased appetite
Psychiatric disorders	Common	depression, irritability
Nervous system disorders	Common	syncope, headache
Cardiac disorders	Common	oedema
	Uncommon	arrhythmia
Gastrointestinal disorders	Common	abdominal pain, vomiting, nausea, constipation, dysgeusia
	Uncommon	pancreatitis, peptic ulcer, rectal haemorrhage, gastritis
Skin and subcutaneous tissue disorders	Common	rash, abnormal skin odor
Renal and urinary disorders	Common	renal tubular acidosis
Reproductive system and breast disorders	Very common	amenorrhea, irregular menstruation
Investigations	Common	Decreased blood potassium, albumin, total protein and phosphate. Increased blood alkaline phosphatase, transaminases, bilirubin, uric acid, chloride, phosphate and sodium. Increased weight

In the study by Nagamani (2015)[52] comparing the patient reported tolerability of sodium phenylbutyrate and GPB the median patient age was 18 years (2 months to 60 years), 51% were adults, 67% were female and 81% were White. The median duration of prior sodium phenylbutyrate was 56 months (0.2 to 300 months). The UCD subtypes were OTC 69%, ASL 13%, ASS1 12%, HHH 3%, ARG1 2%, CPS1 1%. Only 31% had no symptoms and 48% had at least 2 symptoms. The presence or absence of symptoms or symptom severity did not correlate with plasma ammonia levels. Body odour, abdominal pain, vomiting, nausea, burning sensation, heartburn and headache were the most commonly reported symptoms for both products. The baseline is of most relevance for sodium phenylbutyrate but not Pheburane.

The Ammonaps EU Summary of Product Characteristics (SmPC) (sodium phenylbutyrate granules) includes the case report of an 18 year old anorexic patient who developed a

[52]Nagamani S.C.S. Diaz G.A. Rhead W. Berry S.A. et al. Selfreported treatment-associated symptoms among patients with urea cycle disorders participating in glycerol phenylbutyrate clinical trials. Molecular Genetics and Metabolism (2015) 116:1-2 (29-34).

metabolic encephalopathy, lactic acidosis, severe hypokalaemia, pancytopenia, peripheral neuropathy and pancreatitis. A dose reduction resolved all symptoms except recurrent pancreatitis.

Pheburane contains 124 mg of sodium per gram of sodium phenylbutyrate. At the maximum dose of 20 g/day this corresponds to 2.5 g sodium. Oedema has been reported in oncology patients taking sodium phenylbutyrate.

No deaths attributable to sodium phenylbutyrate were included in the submission. Discontinuations due to adverse events were not clearly documented. A review of the PBRER did not reveal any new safety signals.

Laboratory values

In Maestri 1995[46] laboratory studies of electrolytes, haematopoietic, renal and hepatic function were reported to be within normal limits with the exception of slightly elevated aspartate aminotransferase (AST) values. Branched chain amino acids were generally low but arginine was high possibly because of dietary supplementation. Burrage 2014[53] also reported branch chain amino acids lower significantly lower in patients taking sodium phenylbutyrate and although the clinical consequences are unknown suggested patients should be routinely monitored for deficiencies.

Hypokalaemia was reported with high doses of PBA. Hypocalcaemia, hyponatraemia and hyperuricaemia have reported in high doses in oncology patients, although the numbers of patients in the studies with these findings was small. Anaemia has been reported in patients with UCD but also in motor neurone disease. Thrombocytopenia and neutropenia was reported in 1 patient with twice daily infusions of sodium phenylbutyrate in oncology patients with solid tumours

Palatability of the pheburane formulation

Kibleur et al 2014[37] reported a better acceptability of Pheburane than previous treatments in French patients. An evaluations of the palpability of the drug using a100 mm visual analogue scale after 3 consecutive day's repeated dosing, conducted for the previous formulation in a previous survey and a follow-up evaluation was conducted for Pheburane for patients subsequently enrolled in the ATU. In LUC1001 healthy volunteers a statistically and likely clinically significant difference for the characteristics of bitterness and saltiness and overall acceptability for Pheburane over Ammonaps granules tested on a visual analogue scale administered immediately post-dose. The sweetness of the two products was similar.

Post-market safety data

No new safety signals were detected from the post-market data.

Risk management plan

The PSAB has considered RMP version 3 dated 17 January 2017. The sponsor is proposing routine pharmacovigilance and routine risk minimisation activities for its safety concerns. There are several recommendations for the product documents in the post second round RMP report. The sponsor is encouraged to negotiate with the RMP team to resolve these matters.

[53]Burrage. L.C, Jain.M, Gandolfo.L, Lee. B.H, Members of the Urea Cycle Disorders Consortium, and Nagamani.S.C.S. Sodium Phenylbutyrate Decreases Plasma Branched-Chain Amino Acids in Patients with Urea Cycle Disorders. Mol Genet Metab. 113(0): 131–135. 2014

Risk-benefit analysis

Delegate's considerations

The historical rates of survival for UCDs are poor, particularly for neonatal onset disease, and very poor outcomes in terms of cognitive function and growth were expected among survivors prior to treatment options being available. As noted by the clinical evaluator, '*The proposed indication is urea cycle defects (UCDs), which are severe, rare and for which there are few effective therapies for treating the hyperammonaemia. Because of this, sodium phenylbutyrate has become a standard treatment without the support of randomised placebo-controlled trials*.' Sodium phenylbutyrate in various formulations has been available internationally since 1987. Pheburane has been approved in the EU since 2013 and is now available in many countries including Canada and New Zealand. There is already considerable clinical experience with the use of sodium phenylbutyrate for patients with UCDs both internationally and in Australia. In Australia it is accessed through the provisions of schemes for unapproved therapeutic goods.

The sponsor provided a mixed submission heavily reliant on published literature to support the registration of Pheburane for UCDs. Deficiencies within the dossier have been noted by both the clinical and non-clinical evaluators. The sponsor has presented findings for a range of the enzyme disorders within UCDs although the mostly common were ASS and OTC deficiencies.

Although most of the main studies and some of the supplementary references provided supportive PK data there are important gaps. In particular, a lack of robust PK data to support the proposed dosage regimen, an absence of PK data in patients with renal impairment whose renal excretion is important for efficacy, and the absence of data in the elderly, and scant information about drug interactions.

The efficacy of sodium phenylbutyrate was described in the submission in terms of survival, the reduction in the number of hyperammonaemic episodes, cognitive development and growth. Supplementary support arises from the PD findings from plasma ammonia and glutamine levels. The evidence for height and weight suggests that sodium phenylbutyrate does not appear to have a detrimental effect. Changes in height and weight with treatment are confounded by the underlying disease process as are the limited assessments of cognitive development on treatment has not been well characterised. Many of the studies did not include assessment and fewer included follow-up but the information provided is reassuring.

From the sponsor's summary up to 165 patients years of exposure to sodium phenylbutyrate, with safety data from patients with a wide range of conditions beyond UCDs and a spectrum of UCDs. Exposure has been documented in ages ranging from neonates to aged 60. There are limitations to the adverse event report in literature, and therefore limitations to the safety data presented by the sponsor. There may be an underestimation of event types and frequency. The most frequently and consistently reported AEs were menstrual cycle disorders including amenorrhea (23% of menstruating women), decreased appetite, nausea, vomiting, headache, body odour (3% attributed to phenylacetate) and taste aversion. In cancer patients given intravenous sodium phenylbutyrate at higher doses than proposed for UCD neurotoxicity has been reported. PAA levels of 499 to 1285 µg/mL were associated with headache, nausea and vomiting, somnolence. These are common adverse effects of the underlying condition and sodium phenylbutyrate, so rising levels may be missed unless specifically sought.

The sponsor has applied the safety information in the European monographs in its proposed PI for Australia. The source of the some of the adverse effect information is unclear, in particular the haematological abnormalities listed as common and the sponsor has been requested to clarify and to justify the frequency of the reported events.

Hypokalaemia, reduction in branch chain amino acids and reports of elevations of liver function tests (LFTs), although mentioned in the literature are not well characterised and may warrant monitoring. There is a substantial sodium load with sodium phenylbutyrate. Oedema, not frequently reported in the safety set, is a potential adverse effect particularly in older patients.

UCDs require long term therapy, and compliance is most important to reduce the risk of hyperammonaemia crises and the risk of increased disability or death. These disorders affect children and the initiation of waste nitrogen removal therapy often starts in infancy or early childhood. A palatable formula is very important not only for compliance for efficacy but for the quality of life of the patient and carers.

Taking into consideration the nature of UCDs, the importance of alternative waste nitrogen scavenging for the management of hyperammonaemia and increased glutamine in these conditions, the absence of an approved treatment in Australia, the data presented, the long history of use internationally of sodium phenylbutyrate including some years of use of Pheburane in the EU and pending the advice of the ACM, the Delegate is minded to approve the application.

Indication

Although the most robust data are derived from patients with OTC and ASS, similar numbers of patients to those with CPS1 are included in the data set. It is unclear why the indication should include CPS1 but exclude other similarly very rare conditions. The mechanism of action would be the same for all of these patients and there is not anticipated difference in risk. The ACM is requested to comment on this matter. Subject to the advice from the ACM a broader indication of *'Pheburane (sodium phenylbutyrate) is indicated for the management of hyperammonaemia associated with urea cycle disorders. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, and protein-free calorie supplements)'* is proposed.

Dose

Dosing is mostly based on theoretical considerations since there were no dose-finding studies. The clinical evaluator recommended a post-marketing pharmacokinetic study using a sparse-sampling technique to better characterise the dose-concentration relationship over the proposed dosing range and the sponsor has been requested to comment.

Data deficiencies

The submission has a number of deficiencies, some of which are attributable to the rarity of the condition and the challenges of a literature based submission. The nonclinical data are incomplete and were considered insufficient. The lack of pharmacokinetic data in support of the proposed dosing regimen is a deficiency.

There are no data in patients with renal failure. This is considered a major deficiency given the renal excretion of the metabolites. There were no data in elderly patients. Most of the pharmacokinetic data are not derived from the proposed sodium phenylbutyrate product.

Summary of issues

This was a mixed submission that relied heavily on literature. The submission was not well integrated. The key issues with this submission were:

- Whether there are pharmacology data to directly support the dosage regimen.

- Whether there is adequate characterisation of drug interactions
- Whether the PD and efficacy data are sufficient to support the submission
- Whether sufficient safety data have been presented

Proposed action

The Delegate had no reason to say, at this time, that the application for sodium phenylbutyrate should not be approved for registration.

Pending advice from the ACM, the following indications are proposed:

> *Pheburane is indication in the management of urea cycle disorders. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, and protein-free calorie supplements).*

Conditions of registration

The following is an outline of the proposed conditions of registration:

- Implement the AUS-RMP version 3 dated 17 January 2017 and any future updates as agreed with the TGA.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The sponsor has relied heavily on surrogate endpoints. Does the ACM consider the evidence sufficiently robust to support the use of sodium phenylbutyrate?
2. Have adequate data or justification been provided to support the proposed dosage regimen?
3. Have the likely drug interactions been adequately characterised?
4. Given the limited data can the efficacy and safety be extrapolated to all patients with UCD or should the indication be restricted to the enzyme deficiencies proposed by the sponsor. Can the ACM please comment on the Delegate's proposed amended indication?
5. Are the proposed dosing instructions sufficiently clear?
6. The sponsor has not provided evidence for its section about additional nutritional management in the Dosage and Administration section. Given the indication, is inclusion of such information warranted in the PI for sodium phenylbutyrate? Can the committee comment on this information in the Australian clinical context?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor

1. The Committee for Medicinal Products for Human Use (CHMP) requested the sponsor conduct studies to demonstrate that administration by nasogastric tube with Pheburane is feasible. Have those studies been conducted. If so, when will the results be available to the TGA?
2. The clinical evaluator found the response to the question about dosing range unsatisfactory. Please explain the basis of the dosing range in the PI.
3. In which study of UCD patients was the exposure 165 patient years?

4. Haematological toxicity is listed as common in AE table proposed for the PI but haematological abnormalities are not included in the table of adverse events with phenylbutyrate in clinical studies for UCDs. Please provide an account of the haematological toxicity identified for UCD patients taking sodium phenylbutyrate. Please include the dose and duration of sodium phenylbutyrate at the time the event was reported and whether it was reversible (for example, on discontinuation of the treatment or reduction of the dose).
5. Please indicate whether further studies are proposed or additional data have been located from the literature to justify the dosage regimen, as suggested by the clinical evaluator. In your response please comment on the clinical evaluator's recommendation of a sparse sampling PK study in the post-approval setting to further characterise the dosage regimen.
6. Please explain the relevance of the precautionary statement in the Pheburane PI warning that the dose of the safety and efficacy of Cholbam in neonates has not been established, and that based on the data a dose of 10 to 15 mg/kg/day is recommended.
7. Please comment on the RMP team's recommendation to include the CMI with the packaging

Response from sponsor

This response provides additional information on issues raised and advice sought from the Advisory Committee on Medicines (ACM) by the TGA Delegate.

Issues raised by TGA delegate

- Whether there are pharmacology data to directly support the dosage regimen.
- Whether there is adequate characterisation of drug interactions
- Whether the PD and efficacy data are sufficient to support the submission
- Whether sufficient safety data have been presented

The above issues relate to perceived data deficiencies in the dossier, noted by both the non-clinical and clinical evaluators. However both evaluators and the TGA Delegate commented as follows:

- 'This may be acceptable for a substance that has had extensive clinical use and is intended for a life threatening condition' (Non-Clinical Evaluation)
- 'The proposed indication is urea cycle defects (UCDs), which are severe, rare and for which there are few effective therapies for treating the hyperammonaemia. Because of this, sodium phenylbutyrate has become a standard treatment without the support of randomised placebo-controlled trials.' (Clinical Evaluation)
- 'Taking into consideration the nature of UCDs, the importance of alternative waste nitrogen scavenging for the management of hyperammonaemia and increased glutamine in these conditions, the absence of an approved treatment in Australia, the data presented, the long history of use internationally of sodium phenylbutyrate including some years of use of Pheburane in the EU, and pending the advice of the ACM the Delegate is minded to approve the application'. (Delegate's Request for ACMs advice)

The sponsor believes that sufficient evidence has been provided to demonstrate efficacy and safety in the rare indication of urea cycle disorders (Orphan Drug approval given by TGA on 13 August 2014).

Furthermore, in pre-submission discussions, the sponsor clearly outlined to the TGA the data available for inclusion in a registration dossier for this Orphan Drug (OD), indicating that a bioequivalence study would be provided for Pheburane and Ammonaps (EU registered product) to allow for the findings of the published literature for Ammonaps to be extrapolated to Pheburane. Bioequivalence had previously been reported for Ammonaps and the US registered product Buphenyl, meaning that clinical data generated for this US product could also be extrapolated to Pheburane. This bridging data strengthens the applicability of the published clinical data to a new product for an OD indication.

Deficiencies in the dossier were identified in pre-submission discussions with the TGA and justified on the basis of the orphan indication and the worldwide clinical experience with the product. The TGA agreed that a literature-based submission was a suitable registration strategy for this OD indication provided the TGA Guidelines for Literature Based Submissions (LBS) were followed. This agreement indicates a recognition by the TGA of the established safety profile of sodium phenylbutyrate over several decades of clinical use and the fact that a sponsor-conducted complete clinical trial program of randomised, controlled studies would never be conducted, either on ethical grounds or patient availability, based on the clinical data that already existed in the published literature. On this same basis, pharmacodynamic, pharmacokinetic or drug interaction studies specific to the Pheburane formulation were not likely to be conducted in this orphan indication.

For the information of ACM members, the clinical data provided in this current application for both paediatric and adult patients is shown in the following Table 21. A total of 198 paediatric and adult patients were treated with sodium phenylbutyrate, including 25 with the Pheburane formulation. The FDA Summary of Approval refers to 185 patients treated overall in the studies conducted by Maestri et al in the US and Canada and the summary of their findings is included in the Clinical Trials section of the proposed Pheburane Product Information. Overall, the available clinical data represents significant patient numbers in an OD indication and the published results are in line with current clinical practice.

Table 21: Clinical Publications included in Pheburane dossier

Reference	*Population*	*N*	*Design*	*UCD subtype*				
				OTC	**CPS1**	**ASS**	**ASL**	**Other**
Maestri 1991	Neonates	32	Prospective, open label - infants identified as 'at risk' of UCD	20	6	4	2	
Maestri 1995	Infants	24	Long term, open label, 5 and 10 year survival data					ASD: 24
Maestri 1996	Paediatric, girls Age 1 to 17 years	32	Long term, open label, 5 survival data	32				
Kibleur, 2016	Paediatric / adult Mean (SD) age 12.6 (13.0) yrs	25	Phase 4, open label French compassionate use study	15	2	5	1	HHH: 1 LPI: 1
Lee 2010	Adult UP-1204-003	14	Phase 2, open label, fixed sequence crossover – 7 days	12		1		HHH: 1
Diaz 2011	Adult HPN-100-006	45	Pivotal, randomised, DB, crossover, active controlled – 14d	40	2	3		
Lichter-Konecki 2011	Paediatric HPN-100-005	11	Phase 2, open label, fixed sequence crossover – 7 days	9		1	1	
Smith 2013	Paediatric HPN-100-012	15	Phase 2, open label, fixed sequence crossover – 10 days	3		3	8	ARG: 1

Advice sought from ACM

1. *The sponsor has relied heavily on surrogate endpoints. Does the ACM consider the evidence sufficiently robust to support the use of sodium phenylbutyrate?*

The true endpoints for urea cycle disorders could be:

- Improved survival rate
- Prevention or reduction in severity of brain damage

- Improved stature-ponderal growth
- Increased protein tolerance
- Reduction or elimination of hyperammonaemic episodes

For the clinical studies included in this application, surrogate endpoints include blood ammonia, blood and urine metabolites, amino acid levels and long-term ammonia control. Additionally, many studies have also investigated the true endpoints of

- Number of hyperammonaemic crises
- Survival
- Patient growth
- Patient developmental progress

2. *Have adequate data or justification been provided to support the proposed dosage regimen?*

No dose-finding study has been performed in UCD patients. The proposed daily dosage was derived on the basis that one mole of phenylbutyrate will be metabolised to one mole of phenylacetylglutamine, and on a molar basis phenylacetylglutamine is comparable to urea (each containing two nitrogen moles/mole).

Children (6-24 months of age) receiving a diet of 0.2 g/kg/d of nitrogen (1.25 g/kg/d of protein) have been shown to excrete 0.094 g/kg/d of urea nitrogen, accounting for 47% of dietary nitrogen. Children or adults receiving a low but adequate protein intake excrete 40 to 45% of their dietary nitrogen as urea nitrogen. Therefore, a child receiving 1.25 g/kg/day of protein has the obligatory requirement to synthesize 93 mg/kg/day of waste nitrogen as urea. This requirement can be met by patients with the neonatal form of CPS-I and OTC deficiencies if they receive 600 mg/kg/day of sodium phenylbutyrate which if completely conjugated with glutamine will lead to the excretion of 90 mg/kg/day of phenylacetylglutamine nitrogen.

These theoretical considerations were confirmed in an 8 year-old boy (of 27.2 kg body weight) with neonatal CPS-I. When receiving 12 or 14 g/day of phenylbutyrate, 80 to 90% of the dose appeared in the urine as phenylacetylglutamine and phenylacetylglutamine nitrogen accounted for 42 to 44% of dietary nitrogen. Based on this reasoning, the following regimen is proposed:

- 450 to 600 mg/kg/day in neonates, infants and children weighing less than 20 kg
- 9.9 to 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults.

This dosage regimen has its origins in the pioneering work of Brusilow (1991)[40] and is identical to that approved by European, Canadian, US and New Zealand regulatory agencies and corresponds with that recommended by leading UCD experts in the USA and major review articles. However, it should be noted that the dosing of UCD patients is highly individualised and tailored to reflect the severity of each patient's deficiency in urea synthesis and nutritional requirements.[54] The PK study of Monteleone (2013)[55] included in the TGA dossier is also relevant as it included 79 patients with a wide age range (2 months to 72 years). The highest labelled dose for sodium phenylbutyrate (13 g/m^2/day) was used in dosing simulations to predict phenylacetate exposure for various age groups,

[54] Mokhtarani M, Diaz GA, Rhead W, Lichter-Konecki U, Bartley J, Feigenbaum A, et al.Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders.Mol Genet Metab 2012;107(3):308-14.

[55] Monteleone J.P.R. et al, Population PK analysis of glycerol phenylbutyrate (GPB) and sodium phenylbutyrate(NAPB) in adult and pediatric patients with urea cycle disorders (UCD)Molecular Genetics and Metabolism (2012) 105:3 (343-344).

and in particular, assessing the potential for plasma phenylacetate concentrations in the range reportedly associated with transient adverse events. The median phenylacetate levels were well below 500 µg/mL even at the maximal dose and in the youngest of the patients.

3. Have the likely drug interactions been adequately characterised?

In the absence of specific drug interaction studies conducted with Pheburane, because of the low numbers of potential subjects, the proposed PI alerts the prescriber to potential interactions with other drugs that have been shown to raise plasma ammonia levels such as haloperidol, carbamazepine, phenobarbital, topiramate or corticosteroids. A drug interaction with probenecid is also suggested as this drug may inhibit renal excretion of sodium phenylbutyrate.

4. Given the limited data can the efficacy and safety be extrapolated to all patients with UCD or should the indication be restricted to the enzyme deficiencies proposed by the sponsor. Can the ACM please comment on the Delegate's proposed amended indication?

The sponsor accepts the revised indication suggested by the TGA, that is, widening the indications to all UCD and 'related' diseases (transporters deficiencies such as hyperornithinemia-hyperammonemia-homocitrullinuria (HHH)) as some cases were reported to benefit from the treatment. It must however be noted that the regulatory agencies of the EU, Canada and New Zealand have approved the indication wording as originally proposed by the sponsor.

5. Are the proposed dosing instructions sufficiently clear?

The dosing instructions have been modified following recommendations made by the TGA during the evaluation process and the sponsor believes that the proposed dosing instructions are now clear.

6. The sponsor has not provided evidence for its section about additional nutritional management in the Dosage and Administration section. Given the indication, is inclusion of such information warranted in the PI for sodium phenylbutyrate? Can the committee comment on this information in the Australian clinical context.

The 'Nutritional Management' Section in the PI is included based on approved PI documents approved by the EMA, Health Canada and MedSafe. The Australian Society of Inborn Errors of Metabolism Low Protein Handbook for Urea Cycle Disorders includes the following recommendation for Treatment of UCD which supports the requirement for nutritional supplements in addition to nitrogen scavengers such as sodium phenylbutyrate.

> …….*Arginine and citrulline are amino acids that are made within the urea cycle. In people with urea cycle disorders these amino acids may not be made in sufficient quantity and must be replaced as a medication*. (The ASIEM Low Protein Handbook for Urea Cycle Disorders, p. 1.17)

Conditions of registration

· Implement AUS-RMP version 3.0 dated 17 January 2017 and any future updates as agreed with the TGA

The sponsor provides an assurance that the AUS-RMP V3.0 (dated 17 January 2017) and any future updates as agreed with the TGA, will be implemented post-approval.

Questions for the sponsor

1. The CHMP requested the sponsor conduct studies to demonstrate that administration by nasogastric tube with Pheburane is feasible. Have those studies been conducted. If so, when will the results be available to the TGA?

The results of the study were provided to the TGA in the submitted dossier (in the stability module) and the development report will be made available to TGA on request.

2. *The clinical evaluator found the response to the question about dosing range unsatisfactory. Please explain the basis of the dosing range in the PI.*

Please refer to the sponsor's response to Question 2 'Advice sought from ACM' in relation to the dosing range. No further information is available since the sponsor's response. The dosing range is supported by actual clinical practice in Australia and overseas over many years.

3. *In which study of UCD patients was the exposure 165 patient years?*

The study by Maestri et al (1996)[49] Protocol III studied 28 female patients of age range 1 to 17 years treated with a dose of sodium phenylbutyrate of 400-600mg/kg/day. Table 2 in this publication is replicated below:

Table 22: Hyperammonaemic episodes during treatment of girls with OTC deficiency (Maestri, 1996)

Therapeutic Protocol	# patients	No. of hyperammonaemic episodes	Patient years of treatment	Frequency (Episodes / patient-year)
3 (1987-1996)	28	76	**165**	0.5

4. *Haematological toxicity is listed as common in AE table proposed for the PI but haematological abnormalities are not included in the table of adverse events with phenylbutyrate in clinical studies for UCDs. Please provide an account of the haematological toxicity identified for UCD patients taking* ***sodium phenylbutyrate****. Please include the dose and duration of sodium phenylbutyrate at the time the event was reported and whether it was reversible (for example, on discontinuation of the treatment or reduction of the dose).*

The TGA clinical evaluation report states that 'No significant haematological toxicities were identified in the dossier.' The Module 2.7.4 from the EU dossier lists no haematological AE for the two studies specific to the Pheburane product (BE study and French compassionate use). The additional studies included in the Addendum for the Australian dossier did not report any haematological AEs. However, the approved data sheets for EU, Canada and New Zealand all contain a Table: 'Summary of adverse drug reactions reported in CTs with sodium phenylbutyrate'. These data are derived from the long term (10 year) Phase III clinical trial with in 183 UCD patients in USA and Canada and the following haematological AEs are listed, with the overall caveat that AEs were not collected systematically and assessment of causality was confounded by underlying disease, restricted diet and intercurrent illness.

Table 23: Haematological AEs

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	**Common**	anemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anemia, ecchymosis

The USA label for Buphenyl (sodium phenylbutyrate) lists only the following haematological AEs which occurred in one patient and does not include the table above, possibly due to the fact that causality could not be attributed to sodium phenylbutyrate for the 'common AEs' in the Phase II open label study.

· Hematologic: aplastic anaemia and ecchymosis each occurred in one patient.

The sponsor would prefer to retain the table proposed in the Pheburane PI which lists all reported haematological AEs regardless of causality, for consistency with foreign

regulators who may have evaluated the full AE data set from the US/Canada Phase III CT in 183 UCD patients.

5. *Please indicate whether further studies are proposed or additional data have been located from the literature to justify the dosage regimen, as suggested by the clinical evaluator. In your response please comment on the clinical evaluator's recommendation of a sparse sampling PK study in the post-approval setting to further characterise the dosage regimen.*

The proposed dosage regimen has been used internationally for many years and locally under the Special Access Scheme and found to be efficacious and safe. The rarity of the disease makes it difficult to conduct a study that most practitioners would consider unjustified. An updated search of the published literature has not identified any PK publications additional to those included in the application. Refer to sponsor's response to Question 2 'Advice sought from ACPM' in relation to the dosing range.

As mentioned in the sponsor's response to Question 2 'Advice sought from ACPM' in relation to the dosing range, there is a PK study of Monteleone (2013)[55] which included 79 patients with a wide age range (2 months to 72 years). The highest labelled dose for sodium phenylbutyrate (13 g/m^2/day) was used in dosing simulations, to predict phenylacetate exposure for various age groups, and, in particular, assessing the potential for plasma phenylacetate concentrations in the range reportedly associated with transient adverse events. The median phenylacetate levels were well below 500 µg/mL even at the maximal dose and even in the youngest of the patients. Furthermore, it has been suggested that either 24 hour urinary phenylacetylglutamine or morning spot urine phenylacetylglutamine appears to be a more clinically useful and non-invasive marker, compared with monitoring blood levels of metabolites of sodium phenylbutyrate, for assessing compliance and the need for dose adjustment.[54]

6. *Please explain the relevance of the precautionary statement in the Pheburane PI warning that the dose of the safety and efficacy of CHOLBAM in neonates has not been established, and that based on the data a dose of 10 – 15 mg/kg/day is recommended.*

The sponsor apologises for this oversight and the sentence has now been amended to refer to Pheburane.

7. *Please comment on the RMP team's recommendation to include the CMI with the packaging.*

This is acceptable to the sponsor and will be implemented.

The clinical and nonclinical evaluator's recommendations for PI and CMI revisions have been accepted by the sponsor.

Advisory committee considerations

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Pheburane granules containing 484 mg of phenylbutyrate per gram of granules (in pack size of 174g Pheburane) to have an overall positive benefit-risk profile for the Delegate's amended indication;

Proposed Indication in pre-ACM response:

> *'Pheburane (sodium phenylbutyrate) is indicated for the management of hyperammonaemia associated with urea cycle disorders. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (eg amino acids, arginine, citrulline, and protein free calorie supplements)'*

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- A statement in the Dosage and Administration section of the PI and relevant sections of the CMI to provide advice about additional nutritional management consistent with the PI content in Europe, Canada and New Zealand.
- Remove the dosing tables completely from the Dosage and Administration section ensuring that the mg/kg/day and g/m^2/day dosage recommendations section clearly states that the 'mg' and 'g' refer to sodium phenylbutyrate and that 'Pheburane' contains 483 mg phenylbutyrate per gram of granules. Additional advice for pharmacist preparation of Pheburane solution (50 mg sodium phenylbutyrate per mL) for those unable to ingest granules orally could also be provided in this section.
- There should be a greater emphasis that Pheburane treatment should be initiated, monitored and managed by a specialist medical practitioner experienced in the treatment of urea cycle disorders.
- Add a possible interaction with rifampicin (see answer to Question 3 below).
- Change the wording of the usual total daily dose to 'up to of 600 mg/kg and 'up to 13.0 g/m^2' in the Dosage and Administration section of the PI.
- In the Adverse effects section should be revised for consistency in the use of 'adverse event' and 'adverse reaction'.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *The sponsor has relied heavily on surrogate endpoints. Does the ACM consider the evidence sufficiently robust to support the use of sodium phenylbutyrate?*

The ACM noted that the robustness of evidence presented is not optimal, with reliance on surrogate endpoints of blood ammonia, blood and urine metabolites, amino acid levels and long term ammonia control. ACM also noted that some studies reported clinical outcomes such as number of hyperammonaemic crises, survival, growth and developmental progress.

ACM advised that in light of the seriousness, severity and rarity of Urea Cycle Disorders (UCD's), the long history of sodium phenylbutyrate use in UCD's internationally, with an accumulation of data that demonstrates an overall benefit the evidence is sufficient.

2. *Have adequate data or justification been provided to support the proposed dosage regimen?*

The ACM advised that there was not adequate data or justification provided to support the dosage regimen however the proposed dosing regimen is the same as that approved for 'Pheburane' in the EU and Canada. ACM noted that the sodium phenylbutyrate dosage regimen appears to be based on theoretical considerations, rather than any dose-finding

studies (although there was one confirmatory study reported in an 8 year old boy). Further, the ACM noted that the dosing regimen proposes higher doses than usual Australian practice.

3. Have the likely drug interactions been adequately characterised?

ACM advised that the likely drug interactions have not been adequately characterised with no specific drug (or food) interaction studies conducted to date. The ACM noted that the proposed PI provides some guidance on 'potential' drug interactions such as with other drugs known to raise plasma ammonia levels that is consistent with the information for 'Pheburane' internationally.

The ACM noted that the Periodic Safety Update Report (PSUR) from EU reports a case of hepatotoxicity occurring in a 4 year old child who was receiving sodium phenylbutyrate for an 'off-label' indication (progressive familial intrahepatic cholestasis). Reversible hepatotoxicity hypothesised to be possibly due to drug interaction involving rifampicin. This information does not appear in the current PI.

4. Given the limited data can the efficacy and safety be extrapolated to all patients with UCD or should the indication be restricted to the enzyme deficiencies proposed by the sponsor. Can the ACM please comment on the Delegate's proposed amended indication?

The ACM advised that not all patients with UCDhave enzyme deficiencies that result in hyperammonaemia. ACM advised that the enzyme and transporter deficiencies that can result in hyperammonaemia include carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC) and argininosuccinate synthetase (ASS), ornithine translocase deficiency (Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome HHH) and NAGS. The ACM advised that the wording of the proposed indication was appropriate.

ACM noted that to extrapolation to all patients with UCD would be at variance with the approved indications by international regulators.

5. Are the proposed dosing instructions sufficiently clear?

The ACM advised that the dosing instructions were not sufficiently clear. The ACM advised that the presentation of these instructions were potentially confusing and some aspects were potentially error prone and includethe use of the term dosing interval instead of dose range. The committee recommended removing the dosing tables completely.

ACM also noted dosing instructions for liquid medicines should be presented in'mg or 'g' rather than in mL. Additional information can be provided to supplement the dose in 'mg' by also stating the corresponding number of mL to be administered using a solution with a specific strength specified (for example, 50 mg/mL).

ACM noted that dosing advice for neonates is provided in the 'recommended dose' section of the PI but the section on 'Paedatric use' states *'The safety and efficacy of pheburane in neonates has not been established. Pheburane is recommended for infants (> 1 month) age.'* This statement is confusing and should be clarified in the process of PI/CMI negotiations with the TGA, as per proposed conditions of registration above.

6. *The sponsor has not provided evidence for its section about additional nutritional management in the Dosage and Administration section. Given the indication, is inclusion of such information warranted in the PI for sodium phenylbutyrate? Can the committee comment on this information in the Australian clinical context?*

The ACM advised that it is reasonable to provide advice about additional nutritional management in the Dosage and Administration section. The ACM noted that this section is consistent with the content of PI in Europe, Canada and New Zealand. Furthermore, it is also aligned with advice contained in the Australian Society of Inborn Errors of Metabolism Low Protein Handbook for UCD's.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pheburane sodium phenylbutyrate 483 mg/g granule bottle, indicated for:

> *Pheburane (sodium phenylbutyrate) is indicated for the management of hyperammonaemia associated with urea cycle disorders. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, and protein-free calorie supplements)*

Specific conditions of registration applying to these goods

1. The sodium phenylbutyrate AUS-Risk Management Plan (AUS-RMP), version 3 dated17 January 2017, included with submission PM-2016-00417-1-3 , and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The outcomes from exposure to sodium phenylbutyrate during pregnancy are to be discussed as an item of special consideration in the PSURs / PBRERs.

Attachment 1. Product Information

The PI for Pheburane approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au