

5.13 SODIUM PHENYLBUTYRATE, Sugar-coated spheres, 483 mg sodium phenylbutyrate per gram, Pheburane[®], Orpharma Pty Ltd

1 Purpose of application

- 1.1 Authority Required listing for a sugar-coated granule formulation of sodium phenylbutyrate (NaPb) for the treatment of patients with urea cycle disorders (UCD). This drug had not previously been considered by the PBAC.
- 1.2 The submission requested listing on a cost-effectiveness basis compared with standard care comprising other ammonia scavengers, i.e. uncoated NaPb and/or sodium benzoate (NaBz). As the comparators are not PBS-listed or TGA-registered, the submission also presented a comparison that aimed to show the cost-effectiveness of standard care (with ammonia scavengers) versus natural history (without ammonia scavengers).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with UCD and elevated plasma ammonia levels
Intervention	Sugar coated granules of NaPb. Dose: up to 600 mg/kg/day if < 20 kg; up to 13.0 g/m ² /day if > 20 kg. Maximum of 20 g/day. Can be administered in combination with NaBz (lower doses are generally used in combination therapy).
Comparator	<ul style="list-style-type: none"> Standard care with an ammonia scavenger (uncoated NaPb or NaBz), which was compared with coated NaPb monotherapy. As ammonia scavengers can be used in combination, the submission also nominated uncoated NaPb + NaBz as a comparator for coated NaPb ± NaBz. Natural history (no ammonia scavengers), which was compared with standard care.
Outcomes	Survival, hyperammonemic episodes, neurocognitive outcomes, safety
Clinical claim	<p>The submission claimed that :</p> <ul style="list-style-type: none"> ammonia scavengers are life-saving (when used in conjunction with other standard care) compared with natural history; and coated NaPb is more effective than standard care (comprising uncoated NaPb and/or NaBz) at reducing hyperammonemic episodes and their neurocognitive sequelae. The ESC considered this claim was not supported by the evidence provided.

Source: Table 1-1, p1-8 of the submission

NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; UCD = urea cycle disorder

2 Suggested wording for the restriction

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty (pack)	No. of Rpts	Proprietary Name and Manufacturer	
SODIUM PHENYLBUTYRATE 483 mg/g granules, 174g, 4-2	21	5	Pheburane	Orpharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	N/A
Severity:	Patients who have been diagnosed with urea cycle disorder N/A
Condition:	Urea cycle disorders
PBS Indication:	Patients who have been diagnosed with Urea cycle disorders
Treatment phase:	Initial and Continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Patient must be diagnosed as having urea cycle disorder.
Clinical criteria:	Patient must have elevated ammonia levels that are not controlled with diet alone and other adjunct care alone AND Is administered as chronic therapy.
Prescriber Instructions	<i>An increase in the maximum quantity will be authorised to provide for up to one month's supply at a dose of up to 600 mg/kg/day in patients weighing less than 20 kg and up to 13 g/m²/day in patients weighing more than 20 kg.</i>
Administrative Advice	Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at: www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7004 Note No increase in the maximum number of repeats may be authorised. Note No increase in the maximum quantity or number of units may be authorised. Note Special Pricing Arrangements apply.

- 2.2 The submission proposed a Special Pricing Arrangement with an effective dispensed price for maximum quantity of \$ [REDACTED] versus a published price of \$ [REDACTED].
- 2.3 The Pre-PBAC response proposed a [REDACTED] % reduction to the ex-manufacturer price, which would result in an effective dispensed price for maximum quantity of \$ [REDACTED].

3 Background

Registration status

- 3.1 TGA status: sugar-coated NaPb granules were registered by the TGA on 30 May 2017 for:

“the management of hyperammonaemia associated with UCDs. It 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)”.

Rationale for listing

- 3.2 The two currently used ammonia scavengers uncoated NaPb and NaBz, have been used to treat UCDs for decades. They are used as monotherapy or, generally in lower doses, concomitantly. In Australia, they are not TGA-registered and are currently accessed through the Special Access Scheme. The clinician survey indicated that in Australia, public hospitals currently pay for ammonia scavengers via the SAS.
- 3.3 The submission claimed that coated NaPb was superior to uncoated NaPb (tablets, granules and powder) which have a bitter taste that is not easily masked and are unpalatable for some patients. The submission stated that coated NaPb improved compliance and thus, the efficacy of NaPb. The ESC agreed the evidence supported the improved palatability of the coated NaPb compared to the uncoated NaPb however the sub-committee considered there was insufficient evidence to support the efficacy claim made in the submission.
- 3.4 A pharmacokinetic study between coated NaPb and uncoated NaPb granules found the two formulations were bioequivalent, so any differences in efficacy would be due to compliance or study design.
- 3.5 The ESC considered that any advantages arising from increased palatability would not be realised in all patients. The submission did not provide any evidence regarding the proportion of UCD patients who cannot tolerate the uncoated formulations of NaPb. The ESC discussed that this population would predominantly consist of paediatric patients unable to swallow capsules.
- 3.6 The Pre-PBAC response stated that when the key study was conducted (2012-13) there were around 100 patients with UCD receiving uncoated NaPb and that the recruitment of 25 patients who found uncoated NaPb to be unacceptable “suggests a high proportion of patients taking NaPb have difficulty tolerating uncoated NaPb”.
- 3.7 Kibleur 2014 stated (page 413) that the uncoated formulation was generally “acceptable as long as the daily dose is not too high and the age of the patient is compatible with swallowing tablet formulations”. In addition, in the bioequivalence study, 21% of the volunteers (3/14) preferred the taste of the uncoated formulation.
- 3.8 Further, another ammonia scavenger, NaBz is also used in Australia (accessed through the SAS). The submission did not discuss whether NaBz had the same palatability issues as uncoated NaPb. While NaBz is also reported to have a strong bitter taste, it appeared to be tolerable in some of the patients who found uncoated NaPb to be “unacceptable” in Kibleur 2014. The clinician survey presented in the submission

indicated that NaBz tastes better than uncoated NaPb. Thus, the clinical advantage of coated NaPb versus NaBz was uncertain.

- 3.9 If there are patients who are refractory to NaBz and also unable to be administered uncoated NaPb, the evaluation considered that a claim of superiority may have been appropriate for this proportion of the population. However, the submission did not provide justification that a refractory population exists (and it was uncertain what proportion of patients this would represent).
- 3.10 The submission's clinician survey indicated that most neonates with UCD have a naso-gastric tube until six months of age. In these patients, it was unclear from the submission whether hospitals would use the TGA-registered product or an unregistered powder. The latter would be easier to compound so any advantages of a sugar-coated formulation would not be realised in the early onset population.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Deficiencies of the specific enzymes in the urea cycle can result in the accumulation of ammonia (hyperammonemia) and glutamine. Urea cycle disorders are a heterogeneous group of disorders, where hyperammonemia has different consequences for different people. There are an estimated 10 new cases of urea cycle disorders in Australia each year.
- 4.2 Hyperammonemia causes irritability, sleepiness, confusion and vomiting. Very high levels of ammonia can cause a hyperammonemic crisis (HAC), which is a rapidly progressive, often fatal encephalopathy with cerebral oedema, impaired conscious state, followed by respiratory arrest and death or permanent brain injury.
- 4.3 UCDs are inborn errors of metabolism. The onset and severity is highly variable, dependent on the enzyme deficiency. Neonates with significant mutations can experience a HAC within the first two to three days of life. A high proportion of patients who survive this initial HAC have permanent neurological damage.
- 4.4 UCDs diagnosed after one month of age are referred to as late onset UCD. Children with less severe mutations may present outside the neonatal period or sometimes can remain undiagnosed until adulthood.
- 4.5 Survival estimates vary markedly depending which sub-types and age ranges are included, however five-year survival has been shown to be 30% when patients with early onset disease are included.
- 4.6 Coated NaPb was proposed for use in the chronic management of UCDs. It is used in combination with a low protein diet and, if required, supplementation of essential amino acids, vitamins and minerals. Ammonia scavengers are required on an on-going basis in all patients with early onset UCD and some patients with late onset UCD (depending on the age at diagnosis and whether symptoms are present).
- 4.7 The only cure for UCD is a liver transplant, however these are not common with just 24 performed in patients with UCDs in Australia in the 29 years between 1985 and

2014. Liver transplants should ideally take place before irreversible neurological damage occurs, generally in patients under two years of age.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The comparisons presented in the submission are summarised in Figure 1.

Figure 1: Comparisons presented in the submission



Source: Compiled during evaluation based on Figure 1-1, p1-7 of the submission

NaBz = sodium benzoate; NaPb = sodium phenylbutyrate

- 5.2 The submission nominated standard care as the comparator. Standard care comprised treatment with uncoated NaPb and/or NaBz. The ESC considered that both the capsulated and uncapsulated form of NaPb and NaBz should have been considered as possible comparators. The ESC noted that the raw material could be compounded into capsules by compounding pharmacies in order to mask the unpalatable taste of the products.
- 5.3 Standard care appeared to be the therapy most likely to be replaced in clinical practice. However, of the components of standard care (uncoated NaPb and NaBz) it was not clear which was the more appropriate comparator in the monotherapy setting, noting that NaBz appeared to be less costly than uncoated NaPb. The ESC stated that if the sugar coated granules of NaPb were to be PBS listed, it would likely replace the majority of use of current SAS products. This was discussed to be primarily due to the expected reduction in paperwork for both prescriber, pharmacist and patient and improved palatability of NaPb.
- 5.4 Uncoated NaPb contains the same active ingredient as coated NaPb, but may not be a suitable comparator for all patients due to formulation differences. For patients who find uncoated NaPb unpalatable, NaBz may be the therapy most likely to be replaced. In the submission's clinician survey, the majority of clinicians expressed no overall preference between the two ammonia scavengers.
- 5.5 As the comparators are not PBS-listed or TGA-registered, the submission also nominated natural history (without ammonia scavengers) as a comparator. This comparison was presented against ammonia scavengers as a class (rather than against coated NaPb). This comparison provided useful information regarding the effectiveness and cost-effectiveness of ammonia scavengers.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from the Metabolic Dietary Disorders Association via the Consumer Comments facility on the PBS website. The comments highlighted the challenges of living with a severe UCD, including that children commonly require tube feeding by gastrostomy as their appetites is often poor and the medication not very palatable. The comments also outlined support for any treatments that improve health outcomes.

Clinical studies

6.3 A series of indirect comparisons, generally based on meta-analyses of single arm studies, were used to compare: coated NaPb (\pm NaBz) versus uncoated NaPb (\pm NaBz); uncoated NaPb (\pm NaBz) versus NaBz monotherapy; and ammonia scavengers (uncoated NaPb and/or NaBz) versus natural history (no ammonia scavengers).

6.4 The only study with clinical outcomes for coated NaPb was a before-and-after study comparing uncoated NaPb (the “before” arm) and coated NaPb (the “after” arm): Kibleur 2014 (n = 25 in the before arm; n = 20 in the after arm).

6.5 Two additional key studies were: a series of publications by Maestri that showed patient outcomes as the ammonia scavenger regimens evolved over time (relevant for the comparisons between various ammonia scavengers); and Bachmann 2003, a retrospective comparison of ammonia scavengers versus natural history.

6.6 A range of other single-arm, mostly retrospective studies were included in the meta-analyses.

6.7 Details of the studies presented in the submission are provided in the table below.

Table 2: Key studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Coated NaPb versus uncoated studies		
Kibleur 2014	Kibleur Y, Dobbelaere D, Barth M, Brassier S, Guffon N. Results from a Nationwide Cohort Temporary Utilization Authorization (ATU) survey of patients in France treated with Pheburane [®] (Sodium Phenylbutyrate) taste-masked granules.	Paediatric Drugs 2014; 16 (5): 407-415.
	Kibleur Y, and Guffon, N. Long-Term Follow-Up on a Cohort Temporary Utilization Authorization (ATU) Survey of Patients Treated with Pheburane (Sodium Phenylbutyrate) Taste-Masked Granules.	Paediatric Drugs 2016; 18 (2): 139-144.
LUC1001	Clinical Study Report: An open-label, two-period crossover study to determine the bioequivalence 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.	2012 Lucane Pharma SAS.
	Guffon N., Kibleur Y., Copalu W., Tissen C. and Breitreutz J. "Developing a new formulation for sodium phenylbutyrate."	Archives of Disease in Childhood 2012; 97: 1081-1085.
	Guffon, N., Y. Kibleur, E. Pickup, C. Tissen, J. Breitreutz and A. Pretorius. "Comparison of two sodium phenylbutyrate granule formulations."	Journal of Inherited Metabolic Disease 2012; 35 (Suppl. 1): S46.

Trial ID	Protocol title/ Publication title	Publication citation
	Guffon, N., Y. Kibleur, W. Copalu, C. Tissen and J. Breitreutz. "Development of a taste-masked granule formulation of sodium phenylbutyrate adapted for paediatric use."	Archives of Disease in Childhood 2013; 98(6).
Ammonia scavenger studies		
Maestri combined	European Medicines Agency (EMA) – Scientific discussion for the approval of Ammonaps. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000219/WC500024748.pdf Canadian Agency for Drugs and Technologies in Health (CADTH) Canadian Drug Expert Committee Final Recommendation for Pheburane. Available at: https://www.cadth.ca/sites/default/files/cdr/complete/SR0452_complete_Pheburane-Apr-25_16-e.pdf	2001 2016
Maestri 1991	Maestri N, Hauser E, Bartholomew D, Brusilow S. Prospective Treatment of Urea Cycle Disorders. Maestri N, Hauser E, Brusilow H. Long-term survival of patients with neonatal onset of urea cycle defects (UCD).	Journal of Paediatrics 1991; 119 (6): 923-928. Inborn Errors of Metabolism 1990; A163.
Maestri 1995	Maestri N, Clissold D, and Brusilow S. Long-term survival of patients with argininosuccinate synthetase deficiency.	Journal of Paediatrics 1995; 127 (6): 929-935.
Maestri 1996	Maestri N, Brusilow S, Clissold D, Bassett S. Long-term treatment of girls with ornithine transcarbamylase deficiency.	New England Journal of Medicine 1996; 335 (12): 855-859.
Kido 2012	Kido J, Nakamura K, et al. Long-term outcome and intervention of urea cycle disorders in Japan.	Journal of Inherited Metabolic Disease 2012; 35 (5): 777-785.
Uncoated NaPb studies		
Burlina 2001	Burlina A, Ogier H, Korall H, Trefz F. Long-term treatment with sodium phenylbutyrate in ornithine transcarbamylase-deficient patients.	Molecular Genetics and Metabolism 2001; 72 (4): 351-355.
Diaz 2013	Diaz G, Krivitzy L, Mokhtarani M, Rhead W, Bartley, J et al. "Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate."	Hepatology 2013; 57 (6): 2171-2179.
NaBz studies		
Ibarra-Gonzalez 2010	Ibarra-Gonzalez I, Fernandez-Lainez C, Vela-Amieva M. Clinical and biochemical characteristics of patients with urea cycle disorders in a developing country.	Clinical Biochemistry 2010; 43 (4-5): 461-466.
Matsuda 1991	Matsuda I, Nagata N, Matsuura T, Oyanagi K, Tada K, Narisawa K, Kitagawa T, Sakiyama T, Yamashita F, Yoshino M. Retrospective survey of urea cycle disorders: Part 1. Clinical and laboratory observations of thirty-two Japanese male patients with ornithine transcarbamylase deficiency.	American Journal of Medical Genetics 1991; 38 (1): 85-89.
Combined ammonia scavenger treatment (NaPb + NaBz)		
Choi 2015	Choi J, Lee H, Kim J, Kim G, Kim Y, Cho J, et al. Clinical outcomes and the mutation spectrum of the OTC gene in patients with ornithine transcarbamylase deficiency.	Journal of Human Genetics 2015; 60 (9): 501-507.
Natural history (no ammonia scavengers)		
Nassogne 2005	Nassogne M, Heron B, Touati G, Rabier D, Saudubray J. Urea cycle defects: management and outcome.	Journal of Inherited Metabolic Disease 2005; 28 (3), 407-414.

Trial ID	Protocol title/ Publication title	Publication citation
Uchino 1998	Uchino T, Endo F, Matsuda I. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan.	Journal of Inherited Metabolic Disease 1998; 21 Suppl 1: p. 151-159.
Ammonia scavengers versus natural history		
Bachmann 2003	Bachmann C. Long-term outcome of patients with urea cycle disorders and the question of neonatal screening.	European Journal of Paediatrics, Supplement 2003; 162 (1): S29-S33.

Source: Table 2-4, pp2-17 to 2-20 of the submission; and compiled during evaluation based on the studies included in the meta-analysis. NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; OTC = Ornithine transcarbamylase; UCD = urea cycle disorder

6.8 The features of the key studies are summarised in the table below.

Table 3: Key features of the evidence, coated NaPb (\pm NaBz) vs uncoated Nab (\pm NaBz) vs NaBz vs natural history

Study	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Coated NaPb versus uncoated NaPb						
Kibleur 2014	25 (uncoated NaPb); 20 (coated NaPb)	Before-and-after, OL, retrospective for uncoated NaPb (before); prospective for coated NaPb (after). ~ 6 mths in each arm	Serious	All UCD types. Pts who found uncoated NaPb to be unacceptable.	Taste, ease of administration, hyperammonemic episodes	Hyperammonemic episodes
Different ammonia scavenger regimens: Uncoated NaPb vs NaBz vs uncoated NaPb + NaBz						
Maestri 1996	32	Observational, single-centre; OL from 1981 to 1996, > 3 yrs mean follow-up in most arms	Serious	Female OTC, prior HAC	Hyperammonemic episodes; OS in meta-analysis	Not used
Maestri 1995	24			ASS, neonatal rescue		
Ammonia scavengers versus natural history						
Bachmann 2003	88	Retrospective survey	Serious	All UCD types. Pts treated 1975-1986	OS	Survival
All comparisons						
Meta-analyses	Included Kibleur 2014, Maestri studies, Kido 2012, Burlina 2001, Ibarra- Gonzales 2010, Matsuda 1991, Choi 2015, Nassogne 2005, Uchino 1998 (Diaz 2013 included during evaluation). Assessed frequency of hyperammonemic episodes and OS.					Not used

Source: compiled during the evaluation;

ASS = arginosuccinate synthase; HAC = hyperammonemic crisis; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; OL=open label; OS = overall survival; OTC = Ornithine transcarbamylase; mths = months; pts = patients; UCD = urea cycle disorder.

Comparative effectiveness

Coated NaPb (\pm NaBz) versus uncoated NaPb (\pm NaBz): Kibleur 2014

6.9 Kibleur 2014 recruited patients who found uncoated NaPb to be “unacceptable”. Patients were either unable to take NaPb (even if reformulated) or required special administration due to the taste e.g. by naso-gastric tube or gastrostomy. This was narrower than the proposed PBS population of all patients with UCD. Further, this eligibility criterion meant that some patients in the uncoated NaPb arm may have received sub-optimal doses of NaPb and there were high rates of use of concomitant NaBz (60% in both arms). The ESC noted that the submission did not provide information on the overall unacceptability of the uncoated NaPb beyond the 25 patients included in the after arm of this study.

6.10 The ESC agreed that Kibleur 2014 was considered to have a serious risk of bias as it included a retrospective assessment of hyperammonemic episodes in the six months preceding study entry (while patients were on uncoated NaPb) versus a prospective assessment while patients were on coated NaPb as part of a clinical study. The ESC also agreed that the study design had a high risk of survivor bias and it was not clear how outcome data were collected, particularly in the uncoated NaPb (retrospective) arm where there may have been potential for recall bias.

6.11 The PBAC further considered there was a serious risk of bias and confounding as patients elected to enter the study on the basis that they were having difficulty taking ammonia scavenger therapy.

6.12 Table 4 presents the number of hyperammonemic episodes reported in Kibleur 2014.

Table 4: Results of hyperammonemic episodes in Kibleur 2014

Outcome	Coated NaPb (\pm NaBz)	Uncoated NaPb (\pm NaBz)	Difference (95% CI)
Follow-up	Range: 3-11 months	6 months (retrospective)	
No. of hyperammonemic episodes, n/N (average no. of episodes per patient) ^a	0 / 20 (0)	22 / 24 (0.92)	-0.92 (-1.03, -0.81) episodes per patient (average)
No. of patients who experienced \geq 1 hyperammonemic episode/s, n/N (%) ^a	0 / 20 (0%)	12 / 24 (50%) ^b	-50% (-0.70, -0.30) of patients

Source: Table 2-21, p2-58 of the submission;

CI = confidence interval; ITT = intention-to-treat; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; No. = number; PP = per protocol

^a Calculated using the same method as used in the economic model (also used on p414, Kibleur 2014). The economic model used the ITT population in the uncoated arm versus PP in the coated arm. That is, for the before (uncoated NaPb) arm, it was based on the 24 patients who were included in the study and for whom prior data for this outcome were available (data not available for 1 patient). For the after (coated NaPb) arm, this was based on the 20 patients who received \geq 1 week of treatment. While not methodologically appropriate, this was likely conservative as the 5 excluded patients had fewer hyperammonemic episodes than average in the before arm.

^b The number of hyperammonemic episodes per patient ranged from 0 to 3. In the group of patients who experienced \geq 1 hyperammonemic episode with uncoated NaPb, each patient experienced an average of 1.8 episodes. Of note, there were 3 patients who each experienced 3 hyperammonemic episodes, indicating a refractory patient group.

6.13 The submission stated that uncoated NaPb (\pm NaBz) was associated with an average decrease of 0.9 hyperammonemic episodes per patient per six months. Half of the patients experienced one or more hyperammonemic episodes with uncoated NaPb (\pm NaBz), versus none with coated NaPb (\pm NaBz). However, the comparison was not informative because:

- The study recruited patients who found uncoated NaPb to be unacceptable. The ESC advised that this may have been a refractory population, which would only represent a subset of the population requested for PBS-listing.
- The ESC considered that the hyperammonemic episodes were not adequately defined within the submission. Kibleur 2014 did not provide a definition of hyperammonemic episodes, and there is potential for this to include symptoms that resolve without hospitalisation. None of the studies that reported hyperammonemic episodes stated a standardised protocol for collecting this data, leading to a risk of inaccurate data recording (e.g. a high risk of recall bias in retrospective studies such as the before arm of Kibleur 2014). The European Guidelines state that symptoms can be subtle, particularly after the neonatal

period (i.e. the population in Kibleur 2014), and symptomatic episodes can resolve with nonspecific interventions. It was not possible to determine what proportion of the episodes reported in Kibleur 2014 required hospitalisation.

- The PSCR (p4) stated that the lead author of the Kibleur 2014 study was contacted and it was confirmed that each of the episodes reported were decompensations requiring hospitalisation and would not be left ambulatory without a full check-up. The Pre-PBAC response further stated that, as such, these events would have been documented in the patient’s medical records, reducing the aforementioned risk of recall bias. The lead author in the Kibleur 2014 study is identified in the paper, as also being the medical director at the marketing company of Pheburane® in France. The PSCR (p3) did acknowledge that a weakness of the study was the failure to report the outcomes of the HACs in terms of resources use.

6.14 Follow-up in the coated NaPb arm was shorter for those patients who had the most hyperammonemic episodes when receiving the uncoated NaPb (50% of the patients followed-up for three months had the highest number of hyperammonemic events during the control period). Thus, there was a risk of under-reporting outcomes with coated NaPb in patients with the most severe disease.

6.15 Changes in the ease of administration of NaPb from Kibleur 2014 are reported in the table below, based on the per-protocol population.

Table 5: Ease of administration of coated NaPb versus uncoated NaPb in Kibleur 2014

Outcome	Coated NaPb N = 20 (PP)	Uncoated NaPb N = 20 (PP)
“Normal” oral administration for 6 months: • difficulty with the granularity at 1 st dose but subsequently resumed with no issues; • after 6 months, discontinued due to the granularity of coated NaPb.	20 (100%) 1 (5%) 1 (5%)	
Impossible to take NaPb orally (unclear whether any scavengers were given)		1 (5%)
Administered via naso-gastric tube		4 (20%)
Administered via gastrostomy		1 (5%)
Dose too low to compound easily (unclear what was taken)		1 (5%)
Required re-formulation (e.g. into capsules)		1 (5%)
Impossible or difficult to take NaPb so were treated with NaBz		4 (20%)
Difficult to take NaPb orally (assumed NaPb still taken)		7 (35%)
Not treated before		1 (5%)

Source: Compiled during evaluation based on text p2-58 of the submission; Table 2-33 p2-97 of the submission; Table 2, p412 of Kibleur 2014

NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; PP = per protocol

6.16 The change in formulation allowed all 20 of the patients in the “after” arm to receive NaPb orally, whereas previously: five patients (25%) were administered NaPb via a naso-gastric tube or gastrostomy; one (5%) required reformulation of NaPb; and four (20%) found it impossible or difficult to take NaPb and were given NaBz instead.

6.17 These results would not be representative of UCD patients more generally as this was based on a group of patients who found the uncoated form unacceptable, and for whom a granule formulation was suitable. The submission did not discuss the likely

proportion of Australian patients with UCDs who cannot tolerate the uncoated form, and whether NaBz would be a suitable alternative in these patients.

- 6.18 Overall, the ESC considered that Kibleur 2014 supported the improved palatability of coated NaPb compared with uncoated NaPb, however there was insufficient evidence to support an efficacy claim. The ESC also noted that palatability could potentially be achieved, as an alternative, by compound pharmacy using capsules or syrup.

Uncoated NaPb (± NaBz) versus NaBz monotherapy (Maestri)

- 6.19 The key data for other ammonia scavengers were Maestri (1995 and 1996). These were studies of patients with specific sub-types of UCD who were treated with emerging protocols as new ammonia scavengers became available in the US and Canada over 15 years (1981 to 1996). The data are somewhat akin to an interrupted time series study: prior to 1985 these patients received NaBz monotherapy; between 1984 and 1987 patients received uncoated NaPb + NaBz; and beginning in 1987, patients received uncoated NaPb monotherapy in higher doses.

- 6.20 Table 6 outlines the frequency of hyperammonemic episodes from Maestri (1995 and 1996) as treatment protocols changed over time. In Maestri, hyperammonemic episodes were generally defined as hyperammonemia requiring hospitalisation for intravenous ammonia scavenger therapy.

Table 6: Hyperammonemic episode frequency in Maestri 1995 and 1996

Therapeutic protocol	Years ^a	Patients ^b	Number of HAEs ^c	Total patient-years	Frequency (episodes / patient-year)
Maestri 1995, ASS deficiency, neonatal rescue, born before 1990					
NaBz alone	1980-84	12	41	29	1.4
NaBz + uncoated NaPb	1984-87	7	18	26	0.7
Uncoated NaPb monotherapy	1987+	18	52	72	0.7
Total		-	111	127	0.9
Maestri 1996, girls with OTC deficiency aged 1-17 at enrolment (enrolment 1979 to 1990)					
NaBz alone	1980-84	11	25	35	0.7
NaBz + uncoated NaPb ^d	1984-87	22	32	81	0.4
Uncoated NaPb monotherapy ^d	1987+	28	76	165	0.5
Total		-	133	281	0.5

Source: Tables 2-24 to 2-25, pp2-69 to 2-73 of the submission

ASS = arginosuccinic acid synthetase; HAE = hyperammonemic episodes; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; OTC = ornithine transcarbamylase

^a Years when this was the protocol was used

^b There were a total of 24 patients in Maestri 1995 and 32 patients in Maestri 1996. Patient numbers sum to more than 100% as some patients received changing treatment as protocols evolved over time.

^c Definition of HAEs was generally overnight hospitalisation for intravenous drug therapy.

^d Also included some patients who were treated with sodium phenylacetate rather than NaPb as data were not available separately. NaPb and sodium phenylacetate have similar mechanisms of action.

- 6.21 In both cohorts, uncoated NaPb monotherapy was associated with a lower rate of hyperammonemic episodes than NaBz monotherapy.

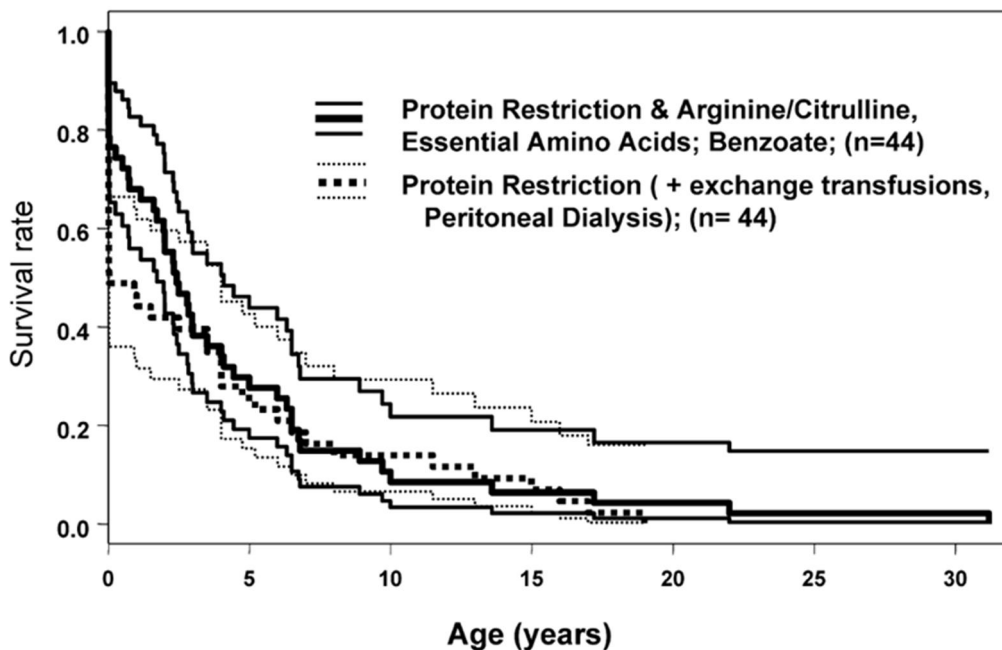
- 6.22 Maestri 1995 stated that strict comparisons between the protocols were difficult due to the variability in the frequency of episodes in individual patients, and the different treatment histories among the patients. Further, each protocol was used in a different

time period so comparisons were confounded by improvements in acute management and co-therapies. NaBz reflected outcomes of patients who entered the study closer to its commencement (risk of survivor bias). Considering these limitations, the claim that uncoated NaPb (\pm NaBz) was superior to NaBz monotherapy was not adequately justified.

Standard care versus natural history (Bachmann 2003)

6.23 Bachmann 2003 was a retrospective survey of European patients with UCD who were treated between 1975 and 1986. It compared patients who had been treated with “old therapy” (protein restriction) versus “new therapy” (ammonia scavengers (generally NaBz) arginine, citrulline, essential amino acids and protein restriction). The survival curves of the old versus new therapies group are presented in Figure 2. Bachmann 2003 included neonates who did not survive their first HAC, so the survival rates are markedly lower than observed in other studies.

Figure 2: Kaplan-Meier OS curves of patients on new therapies (lines) versus old therapies (dotted lines). The outer thinner lines are the corresponding 95% confidence limits.



Source: Figure 3-3, p3-20 of the submission
OS = overall survival

6.24 Survival was improved in the new therapies group up to three years of age, mainly due to improved survival in the newborn group. It was not clear the extent to which chronic ammonia scavenger therapy would have contributed to this compared with other changes over time (e.g. liver transplants, access to acute therapies such as haemodialysis and intravenous ammonia scavengers).

6.25 The Kaplan-Meier curve did not appear to show any increase in survival with new therapies after about four years of age. A key limitation of this analysis was that it did not include the impact of prospective treatment of newborns, i.e. when neonates are treated prior to their first HAC (through newborn screening or in utero diagnosis if at genetic risk). Other limitations included: it was not clear how clinicians recalled the treatments patients received and whether there was overlap in treatments.

Meta-analyses

6.26 The submission presented indirect comparisons based on non-randomised studies to further support the claims shown in Figure 1. These analyses were based on combining and comparing data from studies with distinctly different patient groups (different enzyme deficiencies, patient ages) from different decades (which affects management of acute attacks and co-therapies), and reporting different outcomes. This meant the results from the studies were not comparable. While these meta-analyses were appropriate to include given the lack of other data for patients with this rare disease, the meta-analyses did not allow distinction between direct treatment effects and prognostic effects. In particular, the natural history arm was not informative because it was likely to have included patients who received ammonia scavengers.

Comparative harms

6.27 In Kibleur 2014 no adverse events were reported with coated NaPb, while four patients (16%) reported vomiting reflexes during treatment with uncoated NaPb. This likely reflected the recruitment of patients who found this formulation unacceptable. Longer-term data were available for eight patients from Kibleur 2014 with an average of approximately one year treatment with coated NaPb (range 8 to 30 months). No adverse events were reported in the longer-term follow-up.

6.28 The low patient numbers and before-and-after nature of the study makes any analysis of comparative safety difficult. However, pharmacokinetic data indicated the two formulations were bioequivalent, so differences in safety would not be expected.

Benefits and harms

6.29 The benefits and harms of coated NaPb vs uncoated NaPb is unclear due to the level of uncertainty with the available evidence described above. .

Interpretation of clinical evidence

6.30 The submission claimed that coated NaPb had superior effectiveness and non-inferior safety compared with all comparators (uncoated NaPb, NaBz and natural history).

Coated NaPb (\pm NaBz) versus uncoated NaPb (\pm NaBz)

6.31 The claim that coated NaPb (\pm NaBz) was superior to uncoated NaPb (\pm NaBz) was not well supported by the data presented. The claim was based on a before-and-after study (Kibleur 2014) with small patient numbers and a high risk of bias. Further, the outcome reported (hyerammonemic episodes) may have limited clinical significance.

6.32 Limited safety data were available, however differences in safety between the coated and uncoated formulations would not be expected.

Coated NaPb (\pm NaBz) versus NaBz monotherapy

6.33 The claim of superiority versus NaBz relied on data from Maestri and an indirect comparison based on single arm non-transitive studies. The treatment comparisons differed significantly with respect to known treatment effect modifiers, with the

studies of NaBz monotherapy being from less recent time periods. There were insufficient data to support a claim of superiority over NaBz.

Standard care versus natural history

6.34 The submission also claimed that standard care (with ammonia scavengers) improves survival compared with natural history (no ammonia scavengers). This was not adequately supported by the data presented in the meta-analyses as patients in the natural history arm were likely to have received ammonia scavengers. Bachmann 2003 found that survival was better with standard care in patients up to three years of age, but found no increase in survival after this. It was acknowledged that Bachmann 2003 was a retrospective survey with several limitations. As ammonia scavengers have been used since the early 1980s it was difficult to reliably assess their effectiveness distinct from other changes in the overall management of these patients.

Overall

6.35 The ESC advised that a more appropriate claim may have been that coated NaPb (\pm NaBz) was non-inferior to uncoated NaPb and/or NaBz. Coated NaPb may offer some advantages in the ease of administration in patients who are intolerant to current therapies (e.g. by reducing the need for a naso-gastric tube or gastrostomy, and for compounding of powders).

6.36 If there are patients who are refractory to NaBz and also unable to be administered uncoated NaPb, then a claim of superiority may have been appropriate for this proportion of the population. However, the submission did not provide clinical justification that a refractory population exists.

6.37 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the evidence presented. A claim of non-inferior comparative effectiveness versus other ammonia scavenger formulations would have been appropriate.

6.38 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.39 The submission presented a stepped economic evaluation with three treatment arms:

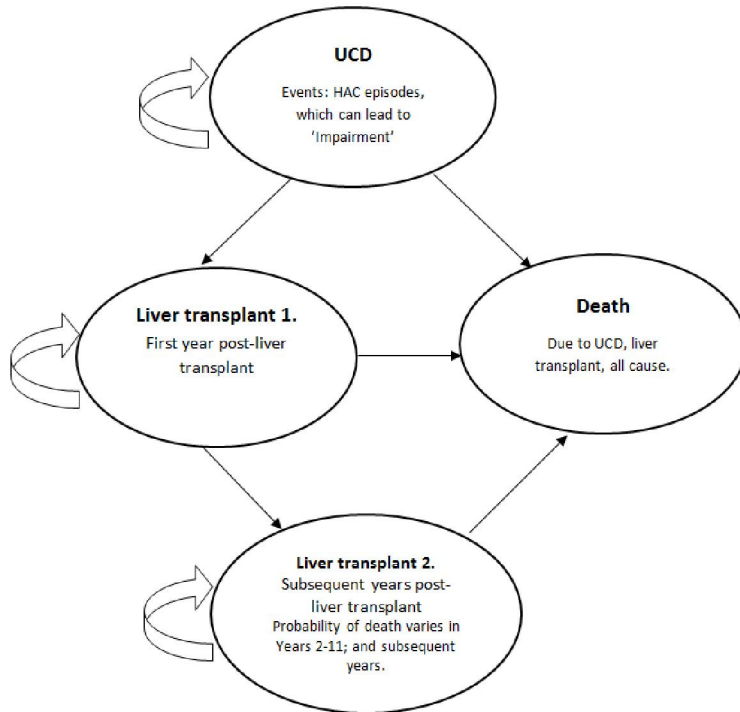
- Coated NaPb (\pm NaBz);
- Standard care with ammonia scavengers, generally informed by uncoated NaPb (\pm NaBz); and
- Natural history with no ammonia scavengers (protein restriction alone in the mid-to-late 1970s and early 1980s).

6.40 The model was largely driven by the clinical data from Kibleur 2014. A more reasonable approach may have been a cost-minimisation analysis against uncoated NaPb and NaBz (potentially weighted for the likely proportion of use of each) incorporating changes in administration-related resource use and costs associated with compounding. The ESC agreed that if there are patients who are refractory to NaBz and also unable to be administered uncoated NaPb, then a cost-utility analysis

may have been appropriate for this proportion of the proposed population. However it is noted that subsequent PBS listing may be difficult in subsidising a medicine for a patient population who would first have to try an unregistered and non PBS subsidised medicine.

6.41 The model structure is outlined in Figure 3 and Table 8.

Figure 3: Simplified structure of the economic model (compiled during evaluation)



Source: Compiled during evaluation. Compared with the submission's diagram (Figure 3-1, p3-9 of the submission), the health states were simplified: the "No previous HAC" state was removed as it was not used in the base case; "Further HACs" was relabelled to "UCD" which better described the state (HACs were events that were not experienced in one arm); the 3 "Death" health states were combined. HAC = hyperammonemic crisis; UCD = urea cycle disorder

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	100 years vs ~6 months in each arm of Kibleur 2014. A 100 year horizon was used to incorporate life expectancy of patients with liver transplants (no incremental costs or benefits were accrued in the liver transplant health states in the coated NaPb versus standard care analysis). Around 90% of patients in the UCD health state were dead within ten years, so the time horizon had almost no impact on the ICER. The clinical data were not sufficiently robust to extrapolate for any length of time.
Outcomes	LYs and QALYs. HACs were an event within the model (associated with a cost), that were based on the rate of hyperammonemic episodes in Kibleur 2014. No evidence was provided to justify the translation of hyperammonemic episodes to crises (the latter would represent a more significant clinical event). The ESC reiterated the difficulty in extrapolating information from Kibleur 2014 as no information about resource use associated with HACs was reported.
Methods used to generate results	Markov model using microsimulations
Health states	<u>UCD</u> : HAC events could occur in this health state, which had a probability of leading to permanent cognitive impairment; <u>Liver transplants</u> : separate states for Year 1 post-transplant and subsequent years; and <u>Death</u> : which could occur due to UCD, liver transplant (higher rates in earlier years post-transplant) and all cause mortality.
Utilities	UCD health state: 0.55; Permanent cognitive impairment: 0.22; Liver transplants: 0.84; Disutility for HACs: -0.50 for 7 days. Based on expert opinion (from a CADTH report) and Guest 2014 (which were in patients with hepatic encephalopathy, a neuropsychiatric disorder caused by liver disease). These were poorly justified (e.g. the utility for permanent cognitive impairment appeared low), however the utilities had minimal impact on the ICER. The ESC noted the lack of reliable utilities in young children.
Cycle length	One year. The ESC advised that one year was too long to represent the frequency of clinical events as patients could have up to 6 HAC events per cycle, with no risk of death.
Transition probabilities	Frequency of HACs was based on hyperammonemic episode rates in Kibleur 2014. UCD-related death was based on Bachmann 2003: coated NaPb and standard care arms used the “newer” therapies group (ammonia scavengers + other co-interventions); natural history arm used the “older” therapies group (protein restriction alone). This significantly overestimated mortality in the relevant population as it included the neonatal period where there is a high risk of death. Liver transplant was based on Batshaw 2014 and Unsinn 2016; 13% probability at age 2 was used in both in the coated NaPb and standard care arms; 0% probability used in natural history arm.
Age of entry into model	Birth (zero years) versus an average age of 12.6 in Kibleur 2014 (affected the dose which was based on mg/kg or mg/m ² dosing).

Source: Compiled during the evaluation from Section 3 of the submission

CADTH = Canadian Agency for Drugs and Technologies in Health; HAC = hyperammonemic crisis; ICER = incremental cost-effectiveness ratio; LY = life year; NaPb = sodium phenylbutyrate; QALY = quality-adjusted life year; UCD = urea cycle disorder

6.42 The key drivers of the economic model are summarised in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Coated NaPb versus standard care		
Rate of HACs	Per Kibleur 2014. All hyperammonemic episodes were assumed to be “crises” (i.e. HACs). Coated NaPb arm: 0 HACs ever; Standard care and natural history arms: Average rate 0.9 HACs per 6 months.	High, favours coated NaPb
Hospitalisation costs for HACs	\$21,432 per HAC in patients <18 years, based on 3 days in ICU, and using 2 AR-DRG codes. Lower hospitalisation costs were used in adults, however the model assumed that few patients with UCD would make it to adulthood.	High, favours coated NaPb
Percent of HACs that required a hospitalisation	Assumed that all HACs required hospitalisation in patients < 18 years.	High, favours coated NaPb
Dose of coated NaPb	Based on avg mg/kg or m ² /kg in Kibleur 2014, then applied to the avg weight of patients in the model, assuming all patients enter the model at birth. Doses per kg (or m ²) of coated NaPb were based on doses given at study entry and thus reflect doses given to patients unable to tolerate NaPb (sub-optimal doses in some patients plus high rates of use in combination with NaBz). Higher doses would be expected in the PBS population.	Moderate, favours coated NaPb
Standard care versus natural history		
Rate of liver transplants	13% probability of a liver transplant at Age 2 in the standard care arm versus 0% chance in the natural history arm.	High favours standard care

Source: Compiled during the evaluation from Section 3 of the submission

AR-DRG = Australian refined diagnosis related group; avg = average; HAC = hyperammonemic crisis; ICU = intensive care unit; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; PBS = Pharmaceutical Benefits Scheme

- 6.43 For coated NaPb versus standard care, the model was almost exclusively driven by the rate of HACs, the cost of the subsequent hospitalisations, and the drug costs (which were influenced by dose and age).
- 6.44 The ESC advised that it was inappropriate to combine both the early onset neonatal population with the late onset paediatric population within the economic model. These patient cohorts have distinctly different disease presentations and resource utilisation will subsequently be different.
- 6.45 The results of the stepped economic evaluation are presented below. The results are based on the price of coated NaPb proposed in the submission (rather than the reduced price proposed in the Pre-PBAC response).

Table 10: Results of the stepped economic evaluation

Step and component	Coated NaPb	Standard Care	Increment
Coated NaPb versus standard care			
Step 1: Study data (Kibleur 2014); 6 month study duration			
Costs	\$ [REDACTED]	\$ [REDACTED] ^a	\$ [REDACTED] ^a
HACs	0	0.9	- 0.9
Incremental cost / HAC avoided			\$ [REDACTED] cost per HAC avoided
Step 2: 10 year time horizon; drug + HAC (hospitalisation) costs only; inclusion of utilities; no discounting			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
HACs	0	8.26	-8.26
QALYs	2.43	2.19	0.24
Incremental cost / HAC avoided			\$ [REDACTED] saving per HAC avoided
Incremental cost / QALY			Dominant
Step 3: Inclusion of liver transplant costs and outcomes			
Costs ^b	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
HACs	0	7.37	-7.37
QALYs	2.89	2.69	0.20
Incremental cost / HAC avoided			\$ [REDACTED] saving per HAC avoided
Incremental cost / QALY			Dominant
Base Case: All costs included; 100-year time horizon; 5% discounting			
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
HACs	0	9.59	-9.59
QALYs	3.58	3.34	0.24
Incremental cost / HAC avoided			\$ [REDACTED] saving per HAC avoided
Incremental cost / QALY			Dominant
Standard care (includes ammonium scavengers) versus natural history (no ammonium scavengers)			
Base Case	Standard care	Natural history	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
HACs	9.59	12.03	-2.44
QALYs	3.34	2.01	1.33
Incremental cost / HAC avoided			\$ [REDACTED] cost HAC avoided
Incremental cost / QALY			\$ [REDACTED]/QALY
Coated NaPb versus natural history (no ammonium scavengers)			
Base Case	Coated NaPb	Natural history	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
HACs	0	12.03	-12.03
QALYs	3.58	2.01	1.57
Incremental cost / HAC avoided			\$ [REDACTED] cost per HAC avoided
Incremental cost / QALY			Dominant

Source: Table 3-8, p3-51 of the submission; Table 3-18, p3-65 of the submission

HAC = hyperammonemic crises; NaPb = sodium phenylbutyrate; QALY = quality adjusted life year

^a Based on NaPb powder (the submission used the cost of NaPb powder in the standard care arm). If the cost of the tablet formulation had been used, the cost in the standard care arm would be \$ [REDACTED], and the incremental cost would be \$ [REDACTED] per HAC avoided.

^b 13% probability of liver transplant at age 2 in both the coated NaPb and standard care arms.

- 6.46 Based on the data from Kibleur 2014, coated NaPb would cost \$ [REDACTED] per hyperammonemic episode avoided in a population who found uncoated NaPb to be “unacceptable”.
- 6.47 For the comparison of coated NaPb versus standard care, the key drivers of the model were the rate of HACs and the cost of the subsequent hospitalisations. The model directly used the rates of hyperammonemic episodes from Kibleur 2014, but assumed each episode represented a HAC (i.e. a crisis, rather than an episode). The ESC considered this issue was not adequately justified in the submission or in the PSCR. Thus, in the coated NaPb arm patients never experienced a HAC, versus an average rate of 0.9 HACs every six months in the standard care arm. This rate was assumed to persist every six months that the patient remained alive (unless the patient received a liver transplant). The ESC agreed that it was unreasonable to assume that these rates would apply to the broader population and that these rates would persist.
- 6.48 Each HAC event was assumed to require a hospitalisation costing \$21,432 (in patients aged under 18 years). This was based on patients spending three days in an Intensive Care Unit per hospitalisation and each episode incurring two AR-DRG admission codes. This significantly overestimated hospitalisation costs. Further, the rate of hospitalisations was not clinically plausible because HACs were based on hyperammonemic episodes which were not defined in Kibleur 2014 and may encompass a broad spectrum of severity; it was not known what proportion of these episodes would require hospitalisation.
- 6.49 Doses of both formulations of NaPb were underestimated compared with doses likely to be used in the Australian population (favoured coated NaPb). The model used the dose of coated NaPb at study entry, thus reflecting doses given to patients who were unable to tolerate NaPb (and thus experiencing poor outcomes). The proportion of patients who had their dose increased during the coated NaPb arm was not known. The doses also reflect high rates of concomitant use of NaBz (lower doses are used in combination therapy). Further, the model assumed all patients entered the model at birth and thus required low doses (versus an average age of 12.6 in Kibleur 2014).
- 6.50 The comparison of standard care versus natural history compared:
- Standard care: the “new therapies” arm of Bachmann 2003 (comprising ammonia scavengers, co-therapies, and more recent practices for the acute management of HACs) plus a 13% probability of a liver transplant at Age 2; versus
 - Natural history: the “old therapies” arm (protein restriction only) of Bachmann 2003 plus a 0% probability of receiving a liver transplant.
- 6.51 Thus, the comparison was broader than the impact of ammonia scavengers alone, and was driven by differences in liver transplants rate. However, the submission did not apply a differential rate of HACs between the two arms.
- 6.52 The key sensitivity analyses conducted by the submission and during evaluation are presented below.

Table 11: Sensitivity analyses presented in submission and conducted during evaluation ^a

	Δ costs	Δ effectiveness	ICER
Coated NaPb versus standard care			
Base case	██████	0.24	██████
<u>Number of HACs in standard care arm</u> (base case: avg 1.8 per year per pt)			
Per Diaz 2013: 0.3 per year (avg)	██████	0.26	██████
Per Maestri 1995: 0.73 per year (avg)	██████	0.27	██████
<u>HAC hospitalisation costs</u> (base case:\$21,432 if <18 yrs)			
\$5,118 (AR-DRG P60A; which was one of the two AR-DRGs used)	██████	0.25	██████
<u>Cost of comparator</u> (base case: uncoated NaPb powder only at \$4.75/g)			
Uncoated NaPb tablets at \$17.60/g	██████	0.25	██████
<u>Dose</u>			
Double the dose of coated and uncoated NaPb and remove NaBz	██████	0.26	██████
<u>Age that patients enter the model</u> (base case: 0)			
7 years (median age in Kibleur 2014)	██████	0.48	██████
<u>Time horizon</u> (base case: 100 years)			
10 years	██████	0.16	██████
Multivariate sensitivity analysis			
50% reduction in hospitalisation costs (\$10,716 per HAC if <18 yrs) and halve probability of HACs in standard care arm (0.9 per year)	██████	0.29	██████
Standard care versus natural history			
Base case	██████	1.33	██████
<u>Liver transplants</u> (base case: 13% in standard care, 0% in natural history)			
13% in both	██████	0.42	██████
0% in both	██████	0.12	██████
<u>Number of HACs per patient</u> (base case: same in both arms at 1.8 per year)			
Increase to 2.2 HACs per year in natural history arm only (20% increase)	██████	1.41	██████
Multivariate sensitivity analyses			
Liver transplant 13% in both arms plus increase in HACs to 2.2 (20% increase) in Natural History arm only	██████	0.50	██████

Source: Constructed during evaluation; Ital = sensitivity analyses conducted during evaluation

AR-DRG = Australian refined diagnosis-related groups; avg = average; HAC = hyperammonemic crisis; ICER = incremental cost effectiveness ratio; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; pt = patient

^a Based on price proposed in the submission (rather than the reduced price proposed in the Pre-PBAC response).

The redacted table shows ICERs in the range of 'dominant' to more than \$200,000/QALY

6.53 For the comparison of coated NaPb versus standard care, the model was most sensitive to changes in the number of HACs per patient, the cost of hospitalisations for HACs and the dose/cost of NaPb (all favoured coated NaPb). For standard care versus natural history, the key drivers of the model were the rate of liver transplants and the number of HACs per patient.

Drug cost/patient/year: \$ ████████ (based on price proposed in Pre-PBAC response)

6.54 The average cost of coated NaPb was based on: the average dose used in Kibleur 2014 of 5.26 g per day; and the dispensed price for maximum quantity proposed in the Pre-

PBAC response of \$ [REDACTED] per pack with 168 g of active drug (\$ [REDACTED]/g). This cost does not include compliance or wastage assumptions. Treatment is life-long.

6.55 The average cost of potential comparators would be:

- Uncoated NaPb tablets: \$33,790 (based on: \$17.60/g). Thus the proposed price of coated NaPb was [REDACTED]% higher than the uncoated tablets.
- Uncoated NaPb powder: \$9,120 (based on: \$4.75/g). The cost of the powder was used in the economic model. Note that this did not include any costs associated with compounding.
- NaBz tablets are \$1.10/g. The equi-effective doses were not discussed in the submission so an average cost could not be determined.

6.56 The ESC noted that the direct costs associated with coated NaPb, uncoated NaPb and NaBz were unable to be verified during the evaluation.

Estimated PBS usage & financial implications

6.57 This submission was not considered by DUSC.

6.58 The submission used a mixed epidemiological and market share approach to estimate the number of patients who would be treated with coated NaPb. Market share assumptions were applied to account for both the market share of NaPb within the ammonia scavenger market and also the share of coated NaPb in the total NaPb market. The submission assumed that the current drug costs for ammonia scavengers, which are not TGA-registered, are currently paid by hospital budgets.

6.59 In the financial estimates, the submission applied the same cost-offsets for hospitalisations due to HACs as per the economic model, except that 25% of patients were assumed to be adults who would require dialysis rather than hospitalisation. (While this was assumed in the economic model, very few patients made it to adulthood in the UCD health state in the economic model).

6.60 The overall share of the total ammonia scavenger market was assumed to be [REDACTED]% in Year 1 and [REDACTED]% in Year 2, which appeared low given the lack of TGA-registered alternatives. The ESC estimated that, if coated NaPb were to be PBS listed, this could lead to an immediate shift from SAS access to PBS subsidised therapy for UCD patients. The ESC considered that product substitution would be closer to 80% reflecting the rate in Kibleur 2014 in the first year. The Pre-PBAC response agreed that uptake would be higher than estimated in the submission and agreed that the financial estimates would need to be revised accordingly.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of coated NaPb						
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Estimated financial implications for increased use of essential amino acids						
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Net financial implications						
Net cost to PBS/RPBS	█	█	█	█	█	█
Reduction in HACs in adults (assumed █% of patients were adults; all patients had 1.8 fewer HACs per year; and each HAC in an adult would require MBS items for dialysis totalling \$█)						
Cost savings to MBS	█	█	█	█	█	█
Net cost to PBS/RPBS/MBS	█	█	█	█	█	█
Hospital costs						
Reduction in HACs in patients aged < 18 years (assumed █% of patients were < 18 years; all patients had 1.8 fewer HACs per year; and each HAC in a patient < 18 years would require a hospitalisation costing \$█)						
Cost savings: hospitalisations	█	█	█	█	█	█
Drug cost savings (reduction in drugs access through the Special Access Scheme)						
Total hospital drug cost savings	█	█	█	█	█	█
Net cost to government	█	█	█	█	█	█

^a Assuming 12 per year as estimated by the submission. Estimates were corrected during evaluation to remove double-counting of the early onset incidence pool

Source: Tables 4-4 to 4-12, pp4-13 to 4-19 of the submission;

HAC = hyperammonemic crisis; MBS = Medicare Benefits Schedule; NaPb = sodium phenylbutyrate; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.61 The submission estimated that the net cost to the PBS/RPBS would be \$30- \$60million over six years.

6.62 The net cost to PBS/RPBS may be different to that estimated because:

- The prevalent population was overestimated because prevalence rates in adults were assumed to be the same as patients aged under 18 (overestimated cost);

- The incident population was added to the prevalent population, despite no survival advantage being claimed against standard care and no rate of death was applied to the prevalent pool (overestimated cost);
- The overall share of the total ammonia scavenger market was underestimated (underestimated cost) as outlined in Paragraph 6.60; and
- Doses were based on Kibleur 2014, while doses in the proposed PBS population would likely be higher (underestimated cost).

6.63 The estimated hospital cost offsets for displacement of NaPb and NaBz may be different as:

- The submission assumed all patients would transfer from uncoated NaPb and that all use of concomitant NaBz would cease (overestimated cost-offsets); and
- The submission off-set the costs of the uncoated NaPb powder and not any of the uncoated NaPb tablets (underestimated cost-offsets).

6.64 Cost offsets for MBS and hospitalisations were significantly overestimated as the rate and costs of hospitalisation for HACs were overestimated.

Quality use of medicines

6.65 Overall it would be expected that coated NaPb would increase compliance for patients who find uncoated NaPb to be unpalatable (e.g. reduce administration times in children and reduce the need for naso-gastric tubes in some patients).

6.66 The PSCR requested that the PBAC consider applying the rule of rescue. The ESC considered that coated NaPb did not meet the necessary criteria because:

- Alternative ammonia scavengers (uncoated NaPb and NaBz) are available in Australia (via the TGA SAS). The Pre-PBAC response argued that this would not be the case if the TGA were to restrict SAS access to other ammonia scavengers;
- The condition is not severe, progressive and expected to lead to premature death in all patients (UCD are a heterogeneous population and severity varies greatly); and
- It is unclear if coated NaPb provides a worthwhile clinical improvement sufficient to qualify as rescue from the medical condition as no overall survival data for coated NaPb were provided.

Per the PBAC Guidelines (Version 5.0), a decision on whether the rule of rescue is relevant is only necessary if the PBAC would be inclined to reject a submission because of its consideration of comparative cost-effectiveness (and any other relevant factors).

6.67 For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of a sugar-coated granule formulation of sodium phenylbutyrate (referred to as coated NaPb) on the basis of unclear

incremental clinical benefit and high incremental cost compared with other ammonia scavenger formulations. In particular, the PBAC considered that the clinical evidence was insufficient to support a claim of superior efficacy versus other ammonia scavenger formulations.

- 7.2 The PBAC considered that ammonia scavengers have an important clinical place in the treatment of UCDS. Thus, the PBAC was of the view that there was a need to ensure the continuing availability of NaPb, which could be achieved through compounding of the raw material into capsules or syrup by compounding pharmacists.
- 7.3 The PBAC considered that other formulations of NaPb and/or NaBz were the appropriate comparators.
- 7.4 The PBAC considered that coated NaPb may be more palatable than uncoated formulations for some patients, predominantly paediatric patients unable to swallow capsules. However, the PBAC considered this taste advantage would not be realised in all patients. For example, the PBAC noted that in a bioequivalence study, 21% of the volunteers (3/14) preferred the taste of the uncoated formulation.
- 7.5 The PBAC considered that the clinical evidence was of low quality and insufficient to support a claim of superior efficacy versus other ammonia scavenger formulations. In particular, the PBAC noted the claim was based on a before-and-after study (Kibleur 2014), which had a serious risk of selection bias as patients were recruited on the basis that they were having difficulty taking ammonia scavenger therapy (i.e. patients were self-selected on the basis of low compliance). If such patients were also preferentially enrolled because of poorly controlled hyperammonemic episodes, regression to the null will also tend to result in overestimation of any benefit. Further, the PBAC considered that the outcome of hyperammonemic episodes was poorly defined in the publication of Kibleur 2014.
- 7.6 The PBAC considered that the evidence provided did not support a difference in health outcomes between the ammonia scavengers. Overall, the PBAC considered that it was inappropriate to extrapolate changes in administration to improved health outcomes.
- 7.7 The PBAC considered that a claim of non-inferior comparative efficacy and safety compared with other ammonia scavenger formulations would have been more appropriate given the clinical evidence available.
- 7.8 Therefore, given the lack of reliable clinical data to inform a cost utility analysis, the PBAC considered that a cost-minimisation analysis against other ammonia scavengers would have been appropriate.
- 7.9 The PBAC considered that market uptake would be considerably higher than estimated in the submission as coated NaPb would likely replace the majority of use of current SAS products. Further, the PBAC considered that the financial estimates had underestimated the dose of coated NaPb and overestimated the cost offsets for hospitalisations, as outlined in Paragraphs 6.60 to 6.64.
- 7.10 The PBAC noted the PSCR's request to apply the rule of rescue. However, the rule of rescue was not relevant in this case as a decision is only necessary if the PBAC would be inclined to reject a submission because of its consideration of comparative cost-

effectiveness (and any other relevant factors). In this case, the PBAC rejected the submission because of its consideration of comparative efficacy (i.e. it considered that the clinical evidence were insufficient to support a claim of superior efficacy versus the nominated comparators). Furthermore, the PBAC considered that coated NaPb would not have met the necessary criteria for the reasons outlined in Paragraph 6.66.

7.11 The PBAC considered that any resubmission should be a major submission made on a cost-minimisation basis against other ammonia scavengers. Revised financial estimates would also need to be provided (as outlined in Paragraphs 6.62 to 6.64 and 7.9).

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The Sponsor will continue working with the PBAC to ensure that this necessary and life changing medication is made available to patients.