7.11 SODIUM PHENYLBUTYRATE, Granules 483 mg (as sodium) per g, 174 g, Pheburane®, Orpharma Pty Ltd

1 Purpose of Application

1.1 The major resubmission proposed an Authority Required listing for a sugar-coated formulation of sodium phenylbutyrate (hereafter referred to as "coated NaPb") for the chronic treatment of patients with urea cycle disorders (UCD). This drug has previously been considered twice by the PBAC. The first submission was considered in November 2017 and the second in March 2018.

1.2 This major resubmission proposed listing coated NaPb as second-line treatment for patients with UCD, who have failed or are intolerant to first-line therapy with sodium benzoate (NaBz). This differed from the previous submissions, which proposed listing coated NaPb as a treatment for patients with UCD in any line of therapy.

1.3 Listing coated NaPb as second-line therapy would not be appropriate as it would "require patients to first try an unregistered and non-PBS subsidised medicine", NaBz (paragraph 6.40, November 2017 Public Summary Document (PSD)). Even though it has been used to treat UCD for decades, NaBz has not been registered anywhere in the world.

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

Component	Description
Population	Patients with symptomatic UCD that require treatment with an ammonia scavenger as part of their standard care, and who: • Have failed treatment on NaBz (50%)[a] or are intolerant to NaBz (36%)[b]; or • Have failed treatment on NaBz and require combination therapy (i.e. NaBz plus NaPb) to control ammonia levels (10-60%)[c, d]
Intervention	Sugar-coated granules of NaPb.
Comparator	Uncoated NaPb
Outcomes	Overall survival, hyperammonemic events, ammonia and glutamine levels and safety.
Clinical claim	Coated NaPb is a second-line treatment in patients with symptomatic UCD that require adjunct treatment with an ammonia scavenger.

Source: Table 1-2, p28 of the March 2019 resubmission
NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; UCD = urea cycle disorder
[a] Unclear source
[b] proportion of total patients on NaBz, based on side effects being reasons for non-adherence reported in Shchelochkov, Dickinson et al. 2016
[c] proportion of total patients on ammonia scavengers based on an Australian clinician survey and a range of values from Kibleur, Dobbelaere et al. 2014, Martin-Hernandez, Aldamiz-Echevarria et al. 2014, Ruegger, Lindner et al. 2014, and Brassier, Gobin et al. 201.
[d] the resubmission assumed that 66% of patients would require NaPb due to failing/being intolerant to NaBz or requiring combination therapy.

2 Requested listing

2.1 Compared to the March 2018 minor resubmission, the changes to the proposed PBS listing were:

- a [redacted]% price reduction in the proposed dispensed price for maximum quantity (DPMQ) from $[redacted] to $[redacted]; and
- the additional clinical criteria that patients must first fail or be intolerant to NaBz as first-line therapy to be eligible for treatment with NaPb (either as monotherapy or in combination with NaBz).

2.2 Consistent with the previous submissions, the resubmission proposed a maximum quantity of two bottles of coated NaPb containing 84 g active NaPb, based on the average dose of 5.26 g/day that patients received in Kibleur 2014. However, the proposed maximum quantity would be insufficient to provide a month's supply of treatment for an Australian patient based on the mean dose derived from TGA Special Access Scheme (SAS) data.

2.3 Based on the TGA NaBz and NaPb SAS applications (July 2017 to June 2018) the mean daily dose for patients was 8.1 g. At this dose, two 84 g bottles of coated NaPb would only be sufficient for approximately three weeks' treatment. The Pre-Sub-Committee Response (PSCR) reported additional data (obtained via an SAS FOI request and not available during the evaluation) that calculated the daily dose at 6.9 g, sufficient for 24 days of treatment. The PBAC noted that this information was not available to be verified during the evaluation process, but considered that it would not affect its decision making.

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

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

Name, Restriction, Manner of administration and form	Max. (pack)	Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
SODIUM PHENYLBUTYRATE 483 mg/g granules, 174g, 2	1		5	$[redacted]	Pheburane	Orpharma

Category / Program	~~Authority Required~~ *GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
~~**Episodicity:**~~	~~N/A~~
~~**Severity:**~~	~~Patients who have been diagnosed with symptomatic urea cycle disorder~~
~~**Condition:**~~	~~Urea cycle disorders~~
PBS Indication:	~~Patients who have been diagnosed with symptomatic~~ Urea cycle disorder*s*
Treatment phase:	~~Initial and Continuing~~ *Initial*

Restriction *Level / Method*:	☐~~Authority Required - In Writing~~ ☒~~Authority Required – Telephone~~ ☒Authority Required – Electronic
~~Treatment criteria:~~	~~Patient must be diagnosed as having symptomatic 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~~ ~~AND~~ ~~Have failed treatment on sodium benzoate or be intolerant of sodium benzoate~~ ~~OR~~ ~~Have failed on treatment with sodium benzoate and require treatment with a combination of sodium benzoate and sodium phenylbutyrate~~
~~Population criteria:~~	~~N/A~~
~~Foreword~~	~~N/A~~
~~Definitions~~	~~N/A~~
Prescriber Instructions	~~N/A~~ *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.*
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 7001~~ ~~Note~~ ~~No increase in the maximum number of repeats may be authorised.~~
~~Cautions~~	~~N/A~~

Category / Program	~~Authority Required~~ *GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
~~Episodicity:~~	~~N/A~~
~~Severity:~~	~~Patients who have been diagnosed with symptomatic urea cycle disorder~~
~~Condition:~~	~~Urea cycle disorders~~

PBS Indication:	~~Patients who have been diagnosed with symptomatic~~ Urea cycle disorder*s*
Treatment phase:	~~Initial and Continuing~~ *Continuing*
Restriction *Level / Method*:	☐~~Authority Required - In Writing~~ ☒~~Authority Required – Telephone~~ ☒Authority Required – Electronic
~~**Treatment criteria:**~~	~~Patient must be diagnosed as having symptomatic urea cycle disorder.~~
Clinical criteria:	*Patient must have previously been issued with an authority prescription for this drug for this condition* ~~AND~~ ~~Is administered as chronic therapy~~ ~~AND~~ ~~Have failed treatment on sodium benzoate or be intolerant of sodium benzoate~~ ~~OR~~ ~~Have failed on treatment with sodium benzoate and require treatment with a combination of sodium benzoate and sodium phenylbutyrate~~
~~**Population criteria:**~~	~~N/A~~
~~**Foreword**~~	~~N/A~~
~~**Definitions**~~	~~N/A~~
Prescriber Instructions	~~N/A~~ *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.*
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 7001~~ ~~Note~~ ~~No increase in the maximum number of repeats may be authorised.~~
~~**Cautions**~~	~~N/A~~

2.5 The PBAC provided the following advice regarding the proposed restriction:

- The restriction level/method should be Authority Required (Streamlined), rather than a telephone authority;
- No definition is required for the term "elevated ammonia";

- Separate initiation and continuing listings are required given the need to have elevated ammonia levels at initiation;
- No specific continuing criteria are required;
- Administrative advice is required to allow for increased quantities;
- Coated NaPb can be prescribed by Nurse Practitioners; and
- Coated NaPb should be exempt from the Early Supply Rule.

3 Background

Registration status

3.1 Coated NaPb was TGA-registered on 30 May 2017 for "the management of hyperammonemia associated with UCDs". Coated NaPb 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).

3.2 For oral administration, both uncoated NaPb (powder or granules) and coated NaPb can be added to food, liquid or water immediately after mixing. For patients requiring administration by nasogastric or gastrostomy tube, uncoated NaPb powder or granules can be mixed with water prior to administration, whereas coated NaPb would require hospital or pharmacy personnel to prepare the solution.

3.3 The proposed PBS-listing was narrower than the approved TGA indication because the proposed PBS-listing required patients to have failed or be intolerant to NaBz as first-line therapy to be eligible for treatment with coated NaPb (either as monotherapy or in combination with NaBz).

Previous PBAC consideration

3.4 This was the third submission for coated NaPb for the treatment of UCD. The first major submission was considered by the PBAC in November 2017 and a minor resubmission was considered by the PBAC in March 2018.

3.5 A summary of the outstanding matters of concern to the PBAC are presented in Table 2.

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

Table 2: Summary of outstanding matters of concern

Component	Matter of concern: Major Submission (November 2017)	Matter of concern: Minor Resubmission (March 2018)	How this was addressed by this Major Resubmission (March 2019)
Prevalent population	230 patients. This was overestimated as the same prevalence rate from patients aged <18 was applied in adults (para 6.62, Nov 2017 PSD).	173 patients. Reduced the prevalent population by 25%; however, the magnitude of adjustment was not justified (para 5.22 PSD)	156 treated patients. Based on the Clinician Survey
Price proposed	Published: $[redacted] Effective (SPA): $[redacted][a] The price was higher than the reduced price proposed in the pre-PBAC response (para 6.45, Nov 2017 PSD).	$[redacted][a], revised the price to the proposed price in the pre-PBAC response for Nov 2017 meeting. The cost of the comparator was significantly overestimated (para 5.14-5.15, Mar 2018 PSD)[b]	$[redacted] ([redacted]% price reduction compared to March 2018). Based on average prices quoted from 7 compounding pharmacies.
Comparator	The PBAC considered NaPb and/or NaBz as the appropriate comparators (para 7.3, Nov 2017 PSD)	Not addressed. Only uncoated NaPb was considered as a comparator.	Amended the clinical placement of coated NaPb to second-line therapy following NaBz. Therefore, the resubmission did not consider NaBz as a comparator.
Economic analysis	A cost effectiveness analysis was conducted. The PBAC considered that any resubmission should be a major submission made on a cost-minimisation basis against other ammonia scavengers (i.e. NaPb and NaBz) (para 7.11, Nov 2017 PSD).	The CMA was conducted at the DPMQ level, using mark-ups, margins and compounding costs that were based on potential prices in the private market rather than those that would be relevant under the PBS (para 5.15, Mar 2018 PSD).	CMA was based on the average cost of obtaining a one-month supply of uncoated NaPb from seven compounding pharmacies across Australia, with utilisation weighted between oral suspension and capsules. The CMA was again conducted at the DPMQ level that used compounding costs that were based on potential prices in the private market.
Dose	5.26 g/day. Based on Kibleur 2014, reflecting the dose of coated NaPb at study entry given to patients who were unable to tolerate uncoated NaPb or with concomitant use of NaBz (thus lower doses). Doses in the proposed PBS population would likely be higher (para 6.49, Nov 2017 PSD)	Increased the doses/day by 20%; however, the magnitude of adjustment was not justified (para 5.22 PSD). Daily dose was approximately 6.61 g/day	Unchanged from November 2017 at 5.26 g/day. The submission argued that this was reasonable given the average age was 12.6 years for the patients in Kibleur 2014. SAS data suggested the mean daily dose of NaPb was 8.1 g/day. The PSCR reported the mean daily dose as 6.9 g/day.

Component	Matter of concern: Major Submission (November 2017)	Matter of concern: Minor Resubmission (March 2018)	How this was addressed by this Major Resubmission (March 2019)
Cost-offsets to hospitals (through SAS)	The cost-offsets for displacement of NaPb and NaBz were overestimated (i.e all patients would transfer from uncoated NaPb and that all use of concomitant NaBz would cease) and was underestimated for excluding the cost-offsets of uncoated NaPb tablets (para 6.63, Nov 2017 PSD).	Revised estimates assuming 50% of patients using NaBz ceased, and uncoated tablets were not offset as it is not readily available. The cost-offsets of formulating coated NaPb into a liquid for patients with a nasogastric tube was not considered (para 5.14, Mar 2018 PSD).	NaBz was not included in cost-offsets in the resubmission. The resubmission did not consider the cost-offsets of compounding coated NaPb for patients with nasogastric tube.

Source: Compiled during the evaluation from Table 1-1, pp23-24, Table 1-2, p28 and Table 1-11, p62 of the March 2019 resubmission, November 2017 PBAC minutes and March 2018 PBAC minutes

Caps = capsules; CMA = cost-minimisation analysis; DPMQ = Dispensed Price for Maximum Quantity; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; OS = oral suspension; para = paragraph; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; SAS = Special Access Scheme; SPA = special price arrangement; UCD = urea cycle disorder

[a] 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] (para 2.3, November 2017 PBAC minutes).

[b] The analysis excluded NaBz as a comparator; included high mark-ups, margins, compounding and wastage costs that were based on potential prices in the private market (para 5.14-5.15, March 2018 PSD).

4 Population and disease

4.1 UCDs are inborn errors of metabolism. The onset (neonatal and late) and severity are highly variable and depend on the type of enzyme deficiency. Early onset (particularly in the neonatal period) and being male was generally indicative of greater disease severity. UCDs can result in the accumulation of ammonia (hyperammonemia) and glutamine, which can cause a hyperammonemic crisis (HAC), resulting in permanent brain injury or death. Ammonia scavengers are used in combination with a low protein diet and, if required, dietary supplements.

4.2 The resubmission identified that coated NaPb should be used as second-line therapy after NaBz. The evaluation and the ESC considered that this was not appropriate in the context of seeking PBS-listing, as NaBz is neither TGA-registered nor PBS-listed. The proportion of UCD patients who would fail or be intolerant to first-line treatment with NaBz, or require combination therapy was assumed to be 66% in the first-year post PBS listing, and increased to 80% in year 6. The evaluation and the ESC considered that this was not well justified.

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

5 Comparator

5.1 The resubmission considered that only uncoated NaPb (compounded into an oral suspension or capsules) was a relevant comparator as it proposed that coated NaPb be limited to second-line therapy. This was not appropriate because:

- The PBAC had previously considered "NaBz was also a relevant comparator" (paragraph 6.3, March 2018 PSD) in any line of therapy since "the TGA had

generally received more SAS applications and notifications for NaBz then for NaPb", and "the majority of [Australian] clinicians expressed no overall preference between the two ammonia scavengers" (paragraph 4.4, March 2018 PSD). The evaluation and the ESC considered that it would be inappropriate to limit use of coated NaPb to second-line therapy, and thus considered that the PBAC's previous comments from March 2018 remained relevant; and

- The ESC had previously considered that the PBS listing of coated NaPb would likely replace the majority of use of NaBz and NaPb in a monotherapy setting, as clinicians would be able to more easily access registered coated NaPb compared to unregistered ammonia scavengers (i.e. NaBz and NaPb) (paragraph 5.3 and 7.9, November 2017 PSD).

  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 a paediatrician via the Consumer Comments facility on the PBS website. The comment outlined that, in current clinical practice, NaBz is used as first line treatment for urea cycle disorders, with the addition of NaPb if required. The clinician considered that NaPb would not replace NaBz. The comments also highlighted the palatability issues with uncoated NaPb and NaBz, and stated that newer preparations are more palatable for children which is important for patient compliance. Additionally, the PBAC noted and welcomed the input from the Metabolic Dietary Disorders Association that highlighted the unpalatability of many current treatments, and that coated NaPb makes treatment easier.

Clinical trials

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

Table 3: 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. 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 2014; 16 (5): 407-415. Paediatric Drugs 2016; 18 (2): 139-144.
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 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.
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.
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.
Nicolaides 2002	Nicolaides, P., D. Liebsch, N. Dale, J. Leonard and R. Surtees. Neurological outcome of patients with ornithine carbamoyltransferase deficiency.	Archives of Disease in Childhood 2002; 86(1): 54-56.

Source: November 2017 Public Summary Document; 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

6.4 To support the clinical placement of coated NaPb as a second-line treatment for UCD, the resubmission presented data from 12 key clinical studies. Among them, only Kibleur (2014) included coated NaPb, whereas uncoated NaPb was used in the other studies. The relevance of these studies to the proposed PBS population is summarised in Table 3 below.

Table 4: The relevance of the March 2019 resubmission's key studies to the proposed PBS

.	Kibleur (2014)	Dobbelaere (2007)[a]	Nicolaides (2002)[a]	Choi (2015)	Burlina (2001)	NaPb vs. GHB[b]	Maestri Publications[c]
Patient numbers	20	187	28	49	9	80 (in total)	183 (Maestri combined)
NaPb mono or in combo with NaPb	Mixed	Not described	NaPb in combo with NaBz	NaPb in combo with NaBz	NaPb mono	NaPb mono	1984-1987 = combo; 1987 + = mono
Match to the PBS population	No – patients were not required to fail NaBz prior to treatment with NaPb.	Unclear – it was uncertain whether patients failed NaBz prior to treatment with NaPb.	Unclear – it was uncertain whether patients failed NaBz first before commencing NaPb as combo.	Unclear – it was uncertain whether patients failed NaBz first before commencing treatment with NaPb as combo therapy.	Yes – patients appeared to be inadequately controlled by NaBz	No – patients were not required to fail NaBz. Further the USA appears to prefer NaPb over NaBz as first-line monotherapy.	No – patients were not required to fail NaBz but were assigned to treatment base on standard of care in the corresponding period.
Presented by Nov 2017 sub	Yes	No	Yes	Yes	Yes	No	Yes

Source: Compiled during the evaluation from Section 2 of the March 2019 resubmission
combo = combination therapy; GHP = glycerol phenylbutyrate; mono = monotherapy; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; Nov = November, PBS = Pharmaceutical Benefits Scheme; sub = submission; USA = United States of America
[a] Studies were excluded by the commentary.
[b] Includes studies comparing uncoated NaPb vs. glycerol phenylbutyrate: HPN-100-006, HPN-100-005, HPN-100-007 and HPN-100-012
[c] Includes studies: Maestri combined, Maestri 1995 and Maestri 1996

6.5 NaPb as monotherapy: The resubmission presented seven studies. Three studies were previously presented in the November 2017 submission (Maestri 1995, Maestri 1996 and Burlina 2001) and four new cross-over studies compared uncoated NaPb to glycerol phenylbutyrate (HPN-100-006, HPN-100-005, HPN-100-007 and HPN-100-012). Among these studies, only Burlina (2001) required patients to use NaBz prior to being enrolled; the trial was for uncoated NaPb. None of the other studies appeared to support NaPb as second-line therapy.

6.6 Combination therapy (i.e. NaPb plus NaBz): The resubmission presented data from five studies. All studies had previously been presented by the November 2017 submission (Kibleur 2014, Maestri combined, Maestri 1995, Maestri 1996, and Choi 2015). Again, none appeared to require NaBz be trialled as first-line therapy before commencing treatment with (coated or uncoated) NaPb.

6.7 Overall, the study populations were unlikely to match the proposed PBS population in either setting (i.e. monotherapy or combination therapy), as none of the included studies (except Burlina 2001) specified the line of therapy of coated or uncoated NaPb. Therefore, there is little evidence to support the use of coated NaPb as second-line therapy in the proposed PBS population.

Comparative effectiveness

6.8 The resubmission presented no new relevant evidence to demonstrate the effectiveness of coated NaPb compared to uncoated NaPb. The PBAC has previously accepted that "a claim of non-inferior comparative efficacy and safety compared with other ammonia scavenger formulations was appropriate" (paragraph 6.4, March 2018 PSD).

Comparative harms

6.9 The resubmission did not present any new evidence to demonstrate the comparative safety of coated NaPb compared to uncoated NaPb. As indicated in the above paragraph, the PBAC has previously accepted that coated NaPb has non-inferior comparative safety versus other ammonia scavenger formulations.

Clinical claim

6.10 The resubmission claimed coated NaPb was non-inferior in terms of efficacy and safety compared to uncoated NaPb (for patients who were intolerant to or inadequately controlled by NaBz or requiring combination therapy).

6.11 The evaluation and the ESC considered that the non-inferiority claim of coated NaPb compared with uncoated NaPb was reasonable when the line of therapy was not specified, since the PBAC has previously accepted the claim based on similar evidence.

6.12 The PBAC considered that the claim of non-inferior comparative effectiveness to uncoated NaPb was reasonable when the line of therapy was not specified.

6.13 The PBAC considered that the claim of non-inferior comparative safety to uncoated NaPb was reasonable when the line of therapy was not specified.

Economic analysis

6.14 Consistent with the March 2018 resubmission, the resubmission presented a cost-minimisation analysis (CMA) based on the cost of NaPb powder compounded into oral suspension and capsules, with utilisation weighted between the two formulations (oral suspension = 53.5% and capsules = 46.5%). The resubmission included the cost of compounding NaPb powder into oral suspension and capsules.

6.15 The implied equi-effective doses were: 1 gram coated NaPb = 1 gram NaPb compounded into an oral suspension or capsule.

6.16 However, compounding NaPb powder into oral suspension or capsules may not be necessary in many cases as:

- the Product Information (PI) for uncoated NaPb powder (p15 of Ammonaps® PI and p5 of Buphenyl® PI) indicated that uncoated NaPb powder or granules can be added to food, liquid or water prior to use; and
- there are uncoated tablet formulations of NaPb available (paragraph 4.2, March 2018 PSD).

6.17 The resubmission derived the approved ex-manufacture price (AEMP) based on a survey of prices quoted for a one month's supply (mean dose = 3.35 g/day) of compounded NaPb power from seven Australian private compounding pharmacies. The resubmission stated that a number of the surveyed pharmacies indicated that they "include higher markups for rarer items to cover the extra cost of specifically purchasing the active ingredient (as they will only purchase small quantities, rather than relatively cheaper bulk supplies) because of the risk of being left with unused or partially used ingredients which they have paid for". However, "the [Australian] clinician survey indicated that in Australia, public hospitals currently pay for ammonia scavengers via the SAS" (paragraph 3.2, November 2017 PSD). Therefore, any compounding of uncoated NaPb would likely take place in public hospitals, where there would likely be more efficiencies of scale (lower marginal cost per bottle compounded) and a different fee structure.

6.18 Table 4 summarises the costs of coated NaPb per gram and for an 84 g bottle using the lowest, median, highest and average quoted price per gram of compounded NaPb.

Table 4: Cost per bottle of coated NaPb using the lowest, median, highest and average price per gram of compounded NaPb.

Weighted cost (oral suspension = 53.5%; capsules = 46.5%)	$ per gram	$ per 84 g bottle
Lowest price (Kingsway Compounding + Your Solution Compounding pharmacy)	$	$
Median price (Sydney Compounding Chemist)	$	$
Highest price (Compounding Australia)	$	$
Average price (AEMP as used by the Resubmission)	**$**	**$**

Source: Compiled during evaluation from Table 3-1, p176 of the March 2019 resubmission
AEMP = approved ex-manufacture price; NaPb = sodium phenylbutyrate;

6.19 The proposed AEMP of $ for an 84 g bottle of coated NaPb was calculated using the average price of $/g for compounded NaPb. However, the evaluation and the ESC considered that this method was not appropriate as:

- The cost was unreasonable, considering almost 80% of the proposed costs of an 84 g bottle of uncoated NaPb powder appeared to be related to compounding fees, mark-ups and/or wastage. The actual cost of 84 g of uncompounded NaPb powder would be $, based on the information provided by the March 2018 resubmission (for 1 kg of NaPb, Table 2, March 2018 PSD);
- The resubmission did not include the cost-offset of compounding of coated NaPb into a liquid solution for patients requiring a nasogastric tube for drug administration, as considered appropriate by PBAC (paragraph 5.14, March 2018 PSD). However, the PSCR stated that the sponsor proposes to provide compounding free of charge to those patients with a nasogastric tube. The PBAC considered that it was unclear how this would work in practice, and would not be feasible in the context of PBS supply arrangements;
- The CMA was conducted at "the DPMQ level [for uncoated NaPb powder], using mark-ups, margins and compounding costs that were based on potential prices in the private market rather than those that would be relevant under the PBS" (paragraph 5.15, March 2018 PSD) and used as the AEMP for coated NaPb; and

- NaBz should have been included as a comparator in the CMA (paragraph 5.14, March 2018 PSD).

6.20 During the evaluation, sensitivity analyses were conducted to address some of the issues identified above (see Table 5). The PBAC noted that the cost of compounded NaPb, based on the uncompounded powder plus the usual PBS compounding fee for extemporaneously prepared benefits would be $[redacted]. The PBAC further noted that if a cost-offset was included for compounding coated NaPb into a liquid solution for the proportion of patients with a nasogastric or gastrostomy tube, the cost would reduce to $487 per 84 g bottle.

Table 5: Comparison of the March 2019 resubmission's method for calculating the AEMP vs. the evaluation's various proposed methods

	Cost per gram	Price per bottle (84 g)
Base case (average quoted price)	$[redacted]	$[redacted]
Sensitivity analyses (per evaluation)		
AEMP based on uncompounded NaPb powder plus PBS compounding fee[a]	$[redacted]	$[redacted]
Proposed AEMP, including cost-offsets for compounding coated NaPb for the proportion of patients with a naso/gas tube[b]	$[redacted]	$[redacted]
International price of coated NaPb (Pheburane)[c]	$[redacted]	$[redacted]

Source: Compiled during evaluation from Table 3-1, p176 of the March 2019 resubmission and the All Wales Therapeutics and Toxicology Centre (2013). AWMSG Secretariat Report - Sodium phenylbutyrate (Pheburane®) –Reference number: 2227, Wales, United Kingdom.
AEMP = approved ex-manufacture price; AWMSG = All Wales Medicines Strategy Group; NaPb = sodium phenylbutyrate; naso/gas = nasogastric or gastrostomy tubes; PBS = Pharmaceutical Benefit Scheme; PSD = public summary document
[a] Calculated based on the cost of $[redacted]/g for 1kg of uncoated NaPb powder extracted from the March 2018 resubmission (Table 2, March 2018 PSD) plus the PBS compounding fee for extemporaneously prepared benefits of $[redacted] (paragraph 5.15, March 2018 PSD).
[b] Using compounding fee ($[redacted]/g) back calculated from costs used in the resubmission for oral suspension. The methodology for this analysis was as follows: The cost of compounded NaPb used in the resubmission assumed an average price of $[redacted]/g and $[redacted]/g for NaPb oral suspension and capsules, respectively. The cost per gram of uncompounded NaPb powder ($[redacted]), extracted from the March 2018 resubmission, was then subtracted from these two results to give the cost of related compounding fees as $[redacted] and $[redacted] respectively. Using the $[redacted] as the cost of compounding coated NaPb into a liquid for nasogastric tubes, a cost-minimisation analysis was conducted that calculated the cost per gram of compounded NaPb for the three different formulations (oral suspension = $[redacted]/g, nasogastric tube = $[redacted] minus $[redacted] = cost-offset of $[redacted]/g, and capsules = $[redacted]/g). Based on the weighted utilisations (oral suspension = 26.75%, nasogastric tube = 26.75% and capsules = 46.5%), an AEMP per gram of coated NaPb was calculated at $[redacted], which resulted in an AEMP per 84 g bottle of coated NaPb of $[redacted].
[c] Derived from a report by the All Wales Therapeutics and Toxicology Centre, which was sponsored by the Wales' National Health Service

Drug cost/patient/year: $[redacted]

6.21 Based on the proposed DPMQ of $[redacted] and an average dose of 5.26 g/day (i.e. 12.57 scripts per patient per year), accounting for 5% wastage, the estimated cost of treatment per patient per year was assumed to be $[redacted]. This was lower than estimated in the March 2018 resubmission ($[redacted] per patient per year) due to a reduction in the proposed price of coated NaPb and a reduction in mean dose (to equal that used in the November 2017 major submission).

6.22 Using the average dose of 8.1 g/day derived from the TGA SAS data and accounting for 5% wastage (i.e. 18.49 scripts per patient per year), the drug costs per patient per year would be $[redacted]. The PSCR disputed these figures, as outlined in paragraph 2.3.

Estimated PBS usage & financial implications.

6.23 This resubmission was not considered by DUSC.

6.24 Consistent with the November 2017 submission, the resubmission used a mixed epidemiological and market share approach to estimate the number of patients who would be treated with coated NaPb.

6.25 The resubmission assumed that 66% of UCD patients would fail or be intolerant to NaBz or would require combination therapy (i.e. NaPb plus NaBz), rising to 80% over four years. However, it was not reasonable for the resubmission to assume an increasing failure rate over time nor to position coated NaPb as second-line therapy.

6.26 The resubmission assumed the listing of coated NaPb would not displace any other PBS listed medications as no other ammonia scavengers are listed on the PBS. This may not be reasonable, as PBS listing may encourage more patients to switch from NaBz to uncoated NaPb as first-line therapy.

Table 6: Estimated use and financial implications for the PBS/RPBS and the government health budget

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed (12.57 per yr)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of coated NaPb to PBS/RPBS						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications of listing coated NaPb to government						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost savings to hospitals (i.e. through SAS)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to government	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Compiled from Tables 4-3 to 4-10, pp189-194 of the March 2019 resubmission and Worksheet Section 4 – Pheburane Base Resubmission Nov 2018.xlsx;
NaPb = sodium phenylbutyrate; PBS = Pharmaceutical Benefits Scheme; resub = resub; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAS = Special Access Scheme; Yr =year; Italics = values were corrected during evaluation (see footnote [a])

[a] The number of patients treated in Table 4-3 and in Section 4 – Pheburane Base Resubmission Nov 2018.xlsx (cells 2a. Patients - epi'!C48:H48) double counted the early onset incident patients. This was corrected during evaluation and all subsequent calculations were based on the corrected patient number. The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.27 The resubmission estimated that the total net cost of listing coated NaPb to the PBS/RPBS would be approximately $20 to $30 million over six years.

6.28 The total cost to the PBS/RPBS was significantly underestimated as:

- Coated NaPb would likely be used in a first-line setting, resulting in a higher utilisation of coated NaPb; and
- The average doses in the proposed PBS population would likely be higher than those given to patients in Kibleur 2014.

6.29 Further, the total cost to the government health budget was significantly underestimated as hospital cost-offsets to the SAS were significantly overestimated as 80% of the proposed savings were mainly due to a reduction in compounding costs, which would unlikely be realised by public hospitals in clinical practice.

6.30 A number of sensitivity analyses were conducted by the resubmission and during evaluation. The total net costs to the PBS/RPBS were most sensitive to increasing the daily dose to the figure derived during the evaluation (8.1 g/day), with the cost increasing from $20 to 30 million to $30 to $60 million over six years.

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 that the proposed clinical place, which was as a second-line therapy after failure and/or intolerability to a medicine that is neither TGA-registered nor PBS-listed (NaBz), was inappropriate, and the cost-minimisation analysis had significantly overestimated the cost of the comparator.

7.2 The PBAC reiterated its previous consideration that ammonia scavengers have an important clinical place, and that there is a need to ensure the continuing availability of NaPb. The PBAC considered that, given there is currently no TGA-approved or PBS-listed product in Australia for this condition, it would be beneficial to list coated NaPb if the above issues were able to be addressed.

7.3 The PBAC noted that the comparator nominated by the resubmission was uncoated NaPb powder compounded into an oral suspension or capsules by a compounding pharmacy. The PBAC reiterated its November 2017 and March 2018 consideration that NaBz was also a relevant comparator.

7.4 The PBAC noted that the resubmission presented no new relevant evidence to demonstrate the effectiveness of coated NaPb compared to uncoated NaPb. The PBAC reiterated its previous consideration that coated NaPb was non-inferior in terms of comparative efficacy and safety compared with other ammonia scavengers (uncoated NaPb and NaBz). The PBAC considered that coated NaPb may be more palatable than uncoated formulations for some patients, predominately paediatric patients unable to swallow capsules. However, the PBAC considered this taste advantage would not be realised in all patients.

7.5 The PBAC noted that the resubmission had calculated the cost of the comparator (NaPb powder compounded into oral suspension and capsules) based on the average price from a survey of seven private compounding pharmacies. The PBAC previously noted (in November 2017) that, in current practice, most NaPb is compounded by hospitals rather than community pharmacies. The PBAC considered that the resubmission's cost-minimisation analysis had significantly overestimated the cost of the comparator because the analysis: included significant costs for compounding,

wastage, mark-ups or other fees that accounted for approximately 80% of the proposed costs; and did not include the cost-offset for compounding the coated tablets into a liquid solution for patients with nasogastric or gastrostomy tubes. Overall, the PBAC considered that the cost-minimisation analysis did not reflect the cost of compounded ammonia scavengers that would be applicable under the PBS.

7.6 The PBAC noted that the evaluation had conducted a sensitivity analysis that included cost-offsets for compounding coated NaPb into a liquid solution for the proportion of patients with a nasogastric or gastrostomy tube, which resulted in a cost of $[redacted] per 84 g bottle (i.e. 57% lower than the requested AEMP for coated NaPb). The PBAC considered that while this would represent a more reasonable cost, it would still overestimate the true comparator cost because it would not address issues such as the exclusion of NaBz in the comparator cost, and the inclusion of significant costs for compounding, wastage and other fees (of around $[redacted] per 84 g bottle).

7.7 The PBAC acknowledged there would be various other methods to calculate offsets for patients with a nasogastric or gastrostomy tube or to calculate the cost of compounding. The PBAC considered that the comparator cost used in the cost-minimisation analysis should be no higher than $[redacted] per 84 g of compounded NaPb.

7.8 The PBAC considered that the financial estimates were underestimated due to the inappropriate assumption that coated NaPb would be used as second-line treatment, and the use of a lower daily dose than would likely be used in the PBS population.

7.9 The pre-PBAC response proposed a subsidisation cap and reimbursement arrangement to address the possibility of clinicians replacing NaBz with coated NaPb. However, the PBAC considered that it would not be appropriate to position coated NaPb as a second-line therapy after failure and/or intolerability to a medicine that is neither TGA-registered nor PBS-listed (NaBz).

7.10 The PBAC considered that a resubmission would need to be made on a cost-minimisation basis against compounded NaPb using the method outlined in Paragraph 7.7 (i.e. resulting in a price no higher than $[redacted] per 84 g bottle of coated NaPb), should not restrict use to the second-line setting, and should update the financial estimates (as outlined in Paragraph 7.9).

7.11 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 to work with the PBAC in order to achieve listing of Pheburane.