

7.20 SODIUM PHENYLBUTYRATE

Granules 483 mg (as sodium) per g, 174 g

Pheburane[®], Orpharma Pty Ltd.

1 Purpose of Application

- 1.1 The minor resubmission requested an Authority Required (STREAMLINED) 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).

2 Requested listing

- 2.1 The requested listing was based on the PBAC’s recommendations from its previous consideration of sodium phenylbutyrate (March 2019 PSD, para 2.5).

- 2.2 The requested pricing for the proposed listing is as follows:

- Approved ex-manufacturer price (AEMP): \$ [REDACTED] (for 1 bottle containing 84 g of active NaPb)
- Price to pharmacy (PtP): \$ [REDACTED]
- Dispensed price for maximum quantity (DPMQ): \$ [REDACTED] (for 3 bottles)

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
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SODIUM PHENYLBUTYRATE 483 mg/g granules, 174g	3	5	\$ [REDACTED]	Pheburane Orpharma
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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Urea cycle disorders
Treatment phase:	Initial treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have elevated ammonia levels that are not controlled with diet alone and other adjunct care alone.
Prescriber Instructions	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/m ² /day in patients weighing more than 20 kg.

Category / Program	GENERAL – General Schedule (Code GE)
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PBS Indication:	Urea cycle disorders
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition.
Prescriber Instructions	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/m ² /day in patients weighing more than 20 kg.

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

3 Background

- 3.1 Coated NaPb was TGA-registered on 30 May 2017 for “the management of hyperammonemia associated with UCDs”. According to the production information (PI), 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 and consumed immediately after mixing. For patients requiring administration by a 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 This drug had previously been considered three times by the PBAC. The first submission was considered in November 2017, the second in March 2018 and the third in March 2019. The key changes compared to the March 2019 submission were that the restriction no longer specified that coated NaPb be used in the second-line setting; the price was reduced by ■% per bottle; and the financial estimates were updated.
- 3.4 In its consideration at the March 2019 meeting, the PBAC advised that a resubmission would need to be made on a cost-minimisation basis against compounded NaPb, resulting in a price no higher than \$■ per 84 g bottle of coated NaPb, and would need to include revised financial estimates. In particular, the PBAC considered that the previous submission underestimated the costs due to the assumption that coated NaPb would be used as a second-line treatment and at a lower daily dose than it would likely be used in the PBS population.
- 3.5 A summary of the previous submissions and current submission are provided in the table below.

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Table 1: Summary of the previous submissions and current submission

Component	Major Submission (November 2017)	Minor Resubmission (March 2018)	Major Resubmission (March 2019)	Current submission (July 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	Unchanged from March 2019 (156 prevalent patients in Year 1 plus 5 grandfathered patients).
Price proposed	\$ [redacted] per bottle AEMP (\$ [redacted] DPMQ for 2 bottles per script).	\$ [redacted] per bottle AEMP (\$ [redacted] DPMQ for 2 bottles per script).	\$ [redacted] per bottle AEMP (\$ [redacted] DPMQ for 2 bottles per script). Based on average prices quoted from 7 compounding pharmacies.	\$ [redacted] per bottle AEMP (\$ [redacted] DPMQ for 3 bottles per script). Based on PBAC advice. This represents a [redacted]% price reduction compared with previous submission ([redacted]% reduction compared with original submission)
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.	No comparator nominated. Use of coated NaPb no longer restricted to the second-line setting.
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.	No formal CMA presented.

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Component	Major Submission (November 2017)	Minor Resubmission (March 2018)	Major Resubmission (March 2019)	Current submission (July 2019)
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. Special Access Scheme data suggested the mean daily dose of NaPb was 8.1 g/day. The PSCR (p4) reported the mean daily dose as 6.9 g/day.	Used the average dose of 8.1 g/day derived from the TGA Special Access Scheme data (during the March 2019 evaluation) and accounted for 5% wastage (i.e. 12.33 scripts per patient per year).
Cost-offsets to hospitals for accessing ammonia scavengers through Special Access Scheme	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).	Based on cost of NaPb plus compounding costs. 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.	Based on cost of NaBz tablets only (no compounding costs included).

Source: Table 2 p 6-7 of March 2019 PSD (Compiled during the March 2019 Evaluation); and Pages 4-7 of the current minor resubmission

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

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 In accordance with PBAC advice, the minor resubmission requested that coated NaPb be used as a first-line therapy for UCD (March 2019 PSD, para 7.10).

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

5 Comparator

- 5.1 The minor resubmission did not nominate a comparator.

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 as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 No clinical trials were presented with this minor resubmission.

Economic analysis

- 6.4 No formal cost-minimisation analysis was presented. The proposed price was consistent with the PBAC's previous advice that the NaPb price should be "no higher than \$█ per 84 g bottle of coated NaPb" (March 2019 PBAC Minutes, paragraph 7.10). This was based on a sensitivity analysis conducted during the March 2019 evaluation 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 \$█ per 84 g bottle.

Drug cost/patient/year: \$█.

- 6.5 The minor resubmission stated that, using the average dose of 8.1 g/day of NaPb (March 2019 PSD, paragraph 2.3 and 6.22) and allowing for 5% wastage, an average of 37 bottles annually would be used per patient. This equated to an average of 12.33 scripts annually at an average cost of \$█ per patient annually (less patient co-payments).

Estimated PBS usage & financial implications

- 6.6 The resubmission revised the utilisation and financial estimates to reflect issues raised by the PBAC in March 2019 as summarised in the table below.

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Table 2: Revised inputs to the utilisation and financial estimates

March 2019 PBAC Minutes	How the resubmission addressed it
<p><u>Price:</u> CMA had significantly overestimated the cost of the comparator (para 7.5, 7.10). AEMP per bottle: \$ [redacted] (\$ [redacted] DPMQ for 2 bottles per script)</p>	<p>Price reduced to \$ [redacted] per bottle AEMP (\$ [redacted] DPMQ for 3 bottles per script).</p>
<p><u>Population:</u> Use of coated NaPb should not be restricted to the second-line setting (para 7.10).</p> <p>Previous submission was for second-line use and assumed:</p> <ul style="list-style-type: none"> - 66% of patients required 'second-line' treatment in Year 1 increasing to 80% in Year 6 (i.e. patients using NaBz who have failed or are intolerant or require combination therapy). - [redacted]% market share in Year 1 increasing to [redacted]% in Year 6. - No grandfathered patients 	<p>First-line listing of coated NaPb.</p> <p>The minor resubmission was for first-line use and assumed:</p> <ul style="list-style-type: none"> - 100% of patients with UCD would be eligible under the proposed listing. - [redacted]% market share in Year 1 increasing to [redacted]% in Year 6 (i.e. assumption that [redacted]% to [redacted]% of eligible patients would utilise coated NaPb thereby displacing NaBz). A sensitivity analysis explored a 90% market uptake rate from year 1. - 5 grandfathered patients. <p>Overall, the number of treated patients was similar to the previous submission despite the current resubmission requesting a broader first-line population (while the previous submission was for second-line use). This was due to the reduced market share assumed in the current resubmission (and the relatively high proportion of patients assumed to require second-line therapy in the previous submission).</p>
<p><u>Offsets:</u> hospital cost-offsets were significantly overestimated as around 80% of the proposed savings were due to a reduction in compounding costs (para 6.29)</p> <p>Offset per patient per year: \$ [redacted] (based on NaPb plus significant compounding costs)</p>	<p>Assumption that only NaBz would be displaced (first-line setting requested). No compounding costs were assumed.</p> <p>Offset per patient per year: \$ [redacted] (based on NaBz tablets, no compounding)</p>
<p><u>Average daily dose:</u> Proposed average daily dose of 5.26 g too low (para 6.21, 6.22).</p>	<p>Used the average dose of 8.1 g/day derived from the TGA Special Access Scheme data and accounted for 5% wastage (i.e. 12.33 scripts of 3 bottles per patient per year).</p>
<p>At a mean daily dose of 8.1 g, two 84 g bottles of NaPb would only be sufficient for approximately three weeks' treatment (para 2.3, 6.22).</p>	<p>Maximum quantity increased to 3.</p>
<p>Double counting of the early onset incident patients (Table 6, note a).</p>	<p>Correction of double counting the early onset incident patients.</p>

6.7 The resubmission stated that the revised estimates assumed that exclusively sodium benzoate (NaBz) would be displaced in the first-line setting. The costing of displaced NaBz was based on pricing for 1 pack of 100 x 500 mg NaBz tablets (obtained from the UK). The sponsor quoted the current price to be £57.39 (obtained from the website www.gpsupplies.com), equivalent to \$105.46 AUD at current exchange rates. It also stated that this price (approximately \$2.11/g) was verified by the increase in requests received by the sponsor to quote and supply NaBz tablets to hospitals in Australia at the time of the submission. The November 2017 submission indicated that the price

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of NaBz tablets was \$ [REDACTED]/g. Further, it was unclear why cost offsets were only assumed for NaBz tablets, rather than a mix of NaBz tablets and NaPb powder. Unlike the previous submission, no hospital compounding costs were included for displaced ammonia scavengers.

- 6.8 The resubmission stated that the equi-effective doses (for determining substitution costs in the financial estimates) were: 1 gram of NaBz approximately equal to 1 gram of NaPb. This therapeutic equivalence was supported by the Kibleur¹ trial, which had an average NaBz dose of 5.72 g/day versus 5.26 g/day for coated NaPb, and the current UCD Guidelines² which suggest dosing of 250 mg/kg/day for both NaBz and NaPb.
- 6.9 The resubmission stated that 3.0 bottles of coated NaPb (84 g per bottle x 3 = 252 g) were roughly equivalent to 5.04 packs of NaBz (1 pack = 100 x 500 mg tablets = 50 g x 5.04 = 252 g). At \$ [REDACTED] per pack, the total cost of NaBz equivalent to 3.0 x 84 g bottles of coated NaPb was quoted to be \$ [REDACTED] per script (excluding importation, distribution and any compounding costs).
- 6.10 The revised utilisation and financial estimates presented in the resubmission are outlined in the table below. It was estimated that the net cost to the PBS/RPBS would be \$10 to \$20 million over six years.
- 6.11 As a minor submission, the changes to the financial estimates were not evaluated.

¹ Kibleur, Y., D. Dobbelaere, M. Barth, A. Brassier and N. Guffon (2014). "Results from a Nationwide Cohort Temporary Utilization Authorization (ATU) survey of patients in France treated with Pheburane((R)) (Sodium Phenylbutyrate) taste-masked granules." *Paediatr Drugs* **16**(5): 407-415.

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488504/>

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Table 3: Updated utilisation and financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent population	■ ^a	■	■	■	■	■
Uptake rate	■%	■%	■%	■%	■%	■%
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed ^b	■	■	■	■	■	■
Net cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Hospital cost savings (offset for NaBz)	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Net cost to Government	\$■	\$■	\$■	\$■	\$■	\$■
Previous submission						
Number of patients treated	■	■	■	■	■	■
Net cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Hospital cost savings (offset for NaPb)	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
Net cost to Government	\$■	\$■	\$■	\$■	\$■	\$■

^a This number includes 5 grandfathered patients

^b Assuming 12.33 scripts per patient per year as estimated by the submission.

Note that Year 1 of the minor resubmission's estimates was 2019.

Source: Table 2-2, p 7 of the minor resubmission, Table 6 March 2019 PSD

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

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS/RPBS would be less than \$10 million.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of a sugar-coated granule formulation of sodium phenylbutyrate (referred to as coated NaPb) for the chronic treatment of patients with urea cycle disorders (UCD). The PBAC recommended the listing at the proposed approved ex-manufacturer price (AEMP) of \$■ per 84 g bottle, which was consistent with the Committee's previous view in March 2019, of the maximum price resulting from the cost-minimisation analysis with compounded NaPb.
- 7.2 The PBAC noted that the resubmission had proposed a revised maximum quantity of three bottles per prescription and considered this appropriate for providing sufficient supply for a month for most patients.
- 7.3 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.

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- 7.4 The PBAC noted that the resubmission did not propose a comparator.
- 7.5 The PBAC noted that the resubmission presented no new relevant clinical 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, predominantly paediatric patients unable to swallow capsules. However, the PBAC considered this taste advantage would not be realised in all patients.
- 7.6 The PBAC noted that the resubmission did not present a formal cost-minimisation analysis and that the proposed price was based on the previous advice that it should be “no higher than \$█ per 84 g bottle of coated NaPb” (March 2019 PBAC minutes, paragraph 7.10). The PBAC noted that the new price had resulted in a █% reduction since the original November 2017 submission.
- 7.7 The PBAC noted the resubmission’s revised average daily dose of 8.1 g/day (derived from the TGA Special Access Scheme data during the March 2019 evaluation) and advised that this was appropriate.
- 7.8 The PBAC noted that the resubmission assumed that only NaBz tablets would be displaced in a first-line setting and did not factor in any compounding costs. The PBAC considered that this was reasonable.
- 7.9 The PBAC noted the estimated \$10 - \$20 million total cost to the PBS over 6 years. The PBAC also noted that, despite the requested listing now being in the first-line setting, the number of treated patients was similar to the previous submission. The PBAC considered this was likely due to the reduced assumed market share in the current submission, and the relatively high proportion of patients assumed to be in the second-line setting in the March 2019 submission.
- 7.10 The PBAC reiterated its previous advice that coated NaPb is suitable for prescribing by Nurse Practitioners.
- 7.11 The PBAC reiterated its previous advice that coated NaPb should be exempt from the Early Supply Rule.
- 7.12 The PBAC advised that sodium phenylbutyrate should not be treated as interchangeable with any other drugs on an individual basis.
- 7.13 The PBAC advised that, because sodium phenylbutyrate is not expected to address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

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Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Proprietary Name and Manufacturer	
SODIUM PHENYL BUTYRATE 483 mg/g granules, 174g	3	5	Pheburane	Orpharma

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Urea cycle disorders
Treatment phase:	Initial treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have elevated ammonia levels that are not controlled with diet alone and other adjunct care alone.
Prescriber Instructions	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/m ² /day in patients weighing more than 20 kg.

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PBS Indication:	Urea cycle disorders
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
Prescriber Instructions	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/m ² /day in patients weighing more than 20 kg.

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PBS Indication:	Urea cycle disorders
Treatment phase:	Grandfathered treatment
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date].
Prescriber Instructions	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/m ² /day in patients weighing more than 20 kg.

9 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.

10 Sponsor's Comment

The sponsor thanks the PBAC for its deliberations and looks forward to making this medication available on the PBS.