

7.20 SODIUM PHENYLBUTYRATE

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

1 Purpose of Application

- 1.1 The minor re-submission requested an Authority Required listing for a sugar-coated granule formulation of sodium phenylbutyrate (NaPb) for the treatment of patients with urea cycle disorders (UCD).
- 1.2 This was the second submission for the sugar-coated granule formulation ('coated NaPb'). The first submission was considered by the PBAC in November 2017.
- 1.3 The key changes since the previous submission were that the economic analysis was revised to a cost-minimisation analysis against NaPb oral suspension or capsules (compounded from the uncoated powder by a pharmacy) and the financial estimates were updated.

2 Requested listing

- 2.1 The requested listing was unchanged from the previous submission.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (pack)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
SODIUM PHENYLBUTYRATE 483 mg/g granules, 174g, 4-2	21	5	\$ [REDACTED] ^a	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 type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
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	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.

^a Updated based on dispensing fees and mark-ups as at February 2018.

- 2.3 The proposed price was unchanged from the previous submission (November 2017 Pre-PBAC response), which had proposed an approved ex-manufacturer price (AEMP) of \$ [REDACTED] per bottle, which equated to a dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] for two bottles. The re-submission did not request a special pricing arrangement.

3 Background

- 3.1 Coated NaPb was TGA-registered 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)”.
- 3.2 This is the second submission for coated NaPb. The first submission was considered at the November 2017 PBAC meeting. The PBAC rejected coated NaPb for PBS listing due to 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 (November 2017 PBAC Meeting Public Summary Document (PSD), para 7.1).
- 3.3 The November 2017 PBAC considered that any re-submission should be a major submission made on a cost-minimisation basis against other ammonia scavengers,

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and that revised financial estimates would also need to be provided (November 2017 PBAC PSD, para 7.11).

3.4 A summary of the outstanding matters of concern to the PBAC are presented in Table 1.

Table 1: Summary of outstanding matters of concern

Component	Matter of concern: November 2017	How the re-submission addressed it
Price proposed	\$██████ per bottle (AEMP) \$██████ per gram of NaPb (at DPMQ level)	Unchanged
Availability of ammonia scavengers through the SAS	[Para 7.2] 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.	The re-submission stated that access to other ammonia scavengers via the TGA SAS program would be more limited now that a registered product (coated NaPb) is available.
Comparator	[Para 7.3] Other formulations of NaPb and/or NaBz were the appropriate comparators.	NaPb powder compounded into oral suspension or capsules by a pharmacy. NaBz was not considered in the CMA, which was not conservative.
Clinical evidence and efficacy claim	[Para 7.5 & 7.7] The PBAC considered the clinical evidence was of low quality and insufficient to support a claim of superior efficacy over other ammonia scavenger formulations. The PBAC considered that a claim of non-inferior comparative efficacy and safety with other ammonia scavenger formulations would have been more appropriate.	No new evidence was provided. The implicit claim was of non-inferior comparative efficacy and safety compared with compounded NaPb given that a CMA was conducted.
Economic analysis	[Para 7.8] Given the lack of reliable clinical data to inform a CUA, a CMA against other ammonia scavengers would have been more appropriate.	CMA versus NaPb powder compounded into oral suspension or capsules by a pharmacy. The PBAC considered that the compounding costs and mark-ups applied were not reasonable.
Financial estimates	[Para 7.10] Market uptake would be considerably higher than estimated as coated NaPb would likely replace the majority of use or current SAS supplied products. Financial estimates had underestimated the dose of coated NaPb and overestimated cost offsets for hospitalisations. (Refer to Table 5 for other concerns and how these were addressed)	Market uptake increased to █████% in Yr 1 increasing to █████% in Yr 5. Doses were increased by █████% (no basis provided). The cost of each hospitalisation was reduced (no change to the number of hospitalisations).

Source: November 2017 PBAC minutes and the re-submission

AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis; CUA = cost-utility analysis; DPMQ = dispensed price for maximum quantity; NaBz = sodium benzoate; NaPb = sodium phenylbutyrate; PBAC = Pharmaceutical Benefits Advisory Committee

Availability of ammonia scavengers via the TGA Special Access Scheme

- 3.5 As outlined in the November 2017 PBAC PSD, the two currently used ammonia scavengers are uncoated NaPb and sodium benzoate (NaBz). These have been used to treat UCIDs for decades. In Australia, they are not TGA-registered and have been accessed through the Special Access Scheme (SAS). The clinician survey provided in the November 2017 submission indicated that in Australia, public hospitals currently access and pay for ammonia scavengers for patients via the SAS.
- 3.6 The re-submission referred to the TGA's "Special Access Scheme: Guidance for Healthcare Practitioners and Sponsors" document, which it stated encourages the use of approved products over unregistered alternatives, referring to the following excerpts:
- "It is expected that the treating health practitioner will have considered all appropriate treatment options that are entered on the ARTG and are currently being supplied prior to considering accessing an unapproved good under the SAS for their patient(s)."
 - "TGA will not consider applications which cite monetary reasons as justification for supply of the unapproved good. The applicant must provide a clinical justification for the use of the good, including why any product on the ARTG and available in Australia is not appropriate for their patient."
- 3.7 The re-submission stated that the TGA was notified that [REDACTED]. Subsequently the TGA notified all prescribers of ammonia scavengers to [REDACTED].

4 Comparator

- 4.1 The comparator nominated by the re-submission was uncoated NaPb powder compounded into an oral suspension or capsules by a compounding pharmacy. In its November 2017 consideration, the PBAC had considered that NaBz was also a relevant comparator in the monotherapy setting.
- 4.2 Further, there are uncoated tablet formulations of NaPb (that have been accessed through the SAS) which would be appropriate in some patients. In its previous consideration, the PBAC noted that the taste advantage of the coated formulation would not be realised in all patients. For example, the PBAC noted that in a bioequivalence study, [REDACTED]% of the volunteers ([REDACTED]) preferred the taste of the uncoated formulation (November 2017 PBAC PSD, para 7.4).
- 4.3 The pre-PBAC response claimed that NaBz was not an appropriate comparator in the monotherapy setting because it is not registered anywhere in the world, is not produced to pharmaceutical grade standards and theoretically has a lower nitrogen

scavenging capacity that NaPb. The pre-PBAC response also re-iterated that it is not a comparator in the combination therapy setting (i.e. where NaPb and NaBz are used concomitantly).

- 4.4 The PBAC noted that the TGA had generally received more SAS applications and notifications for NaBz than for NaPb. The PBAC noted the limitations of these data (e.g. it does not indicate that supply took place), but overall considered it indicated that NaBz was more commonly used than NaPb. Further, the PBAC recalled that in the November 2017 submission's clinician survey, the majority of clinicians expressed no overall preference between the two ammonia scavengers.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from two individuals via the Consumer Comments facility on the PBS website. The comments described the high cost of coated NaPb and clinical need for treatment.

Interpretation of clinical evidence

- 5.3 No new clinical evidence was provided in the re-submission. In its previous consideration, the PBAC considered that the evidence provided did not support a difference in health outcomes between the ammonia scavengers. 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 (November 2017 PBAC PSD, para 7.6 and 7.7).
- 5.4 The re-submission did not make any claims regarding comparative efficacy and safety. However, given that a cost-minimisation analysis was conducted, the implicit claim was of non-inferior comparative efficacy and safety compared with compounded NaPb.
- 5.5 The PBAC re-iterated its previous consideration that a claim of non-inferior comparative efficacy and safety compared with other ammonia scavenger formulations was appropriate given the clinical evidence that had been presented.

Economic analysis

- 5.6 The re-submission presented a cost-minimisation analysis versus compounded NaPb, i.e. uncoated NaPb powder that was compounded into oral suspension or capsules by a pharmacy.
- 5.7 The implied equi-effective doses were: 1 gram coated NaPb = 1 gram NaPb compounded into an oral suspension or capsule.
- 5.8 The re-submission calculated the average cost per gram of NaPb oral suspension or capsules based on the cost of the raw powder plus compounding fees, with utilisation weighted between the two formulations (suspension and capsules). The calculations are outlined in Table 2. The costs were not verified during preparation of the minor overview.
- 5.9 The re-submission stated that the costs were based on: compounding costs from a Sydney-based compounding pharmacy; and pricing of NaPb powder from medisca.com.au.
- 5.10 The quantities formulated for a one-month supply were based on:
- Oral suspension: 60g of NaPb per month (comprising six bottles) The re-submission stated this was a “common sized script” at the [REDACTED] (once made, NaPb suspension has a shelf life of 1 month).
 - Capsules: 150g of NaPb per month (comprising 300 capsules each containing 500mg NaPb). This was based on the average daily dose of 5.26 gm per day in Kibleur 2014 (the key study used in the previous submission).
- 5.11 The re-submission stated that the weighting between the two formulations (oral suspension or capsules) was based on Kaplan-Meier curves from Bachmann (2003). The re-submission assumed that all patients under three years of age would require the oral suspension. In essence, the re-submission assumed that:
- 38% of patients have early-onset UCD, [REDACTED] would require the oral suspension; and
 - 62% of patients have late-onset UCD, [REDACTED]% of whom would require the oral suspension and [REDACTED]% of whom would require the capsules.
- 5.12 Thus, the re-submission assumed that [REDACTED]% of patients would use the oral suspension and [REDACTED]% would use the capsule presentation.

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Table 2: Sponsor derivation of typical one month supply of uncoated NaPb

Calculation	Suspension 100mg/mL	Capsule 500mg	Source/notes for value used in re-submission
Quantity per month	6 x 100mL bottles	300 capsules	
Amount of active NaPb	60g	150g	
NaPb powder	\$546	\$1,092	Medisca price list. Nearest quantity used. The re-submission stated that the prices were: 100g = \$546; 500g = \$1,640; 1kg = \$2,785.
Capsules	█	\$█	Medisca price list
Pharmacist Mark-up	\$█	\$█	\$█ per bottle, \$█ per 100 capsules - compounding pharmacy
Packaging and labelling	\$█	\$█	\$█ per bottle or 100 capsules - compounding pharmacy
Labour	\$█	\$█	\$█ per bottle, \$█ for 300 capsules - compounding pharmacy
Loading for Package Breakage	\$█	\$█	\$█ per bottle or per 100 capsules - compounding pharmacy
Capsblend or suspension syrup	\$█	\$█	Medisca price list
Total Cost	\$█	\$█	
█% margin: overheads + profit	\$█	\$█	Compounding pharmacy
Net Price to Patient	\$█	\$█	
Cost per gram of NaPb	\$█/g	\$█/g	
Weighting	█	█	Literature based
Weighted Average	\$█/g		
Costs of ammonia scavengers not compounded by a community pharmacy			
NaPb powder	\$█/g (uncompounded powder)		Price used in submission (100g = \$█)
NaBz tablets	\$█/g		Source: November 2017 submission

Source: Table 1 p3, Minor re-submission; November 2017 PBAC Minutes, para 6.55

AEMP = approved ex-manufacturer price; AHI = Administration, Handling and Infrastructure

- 5.13 The re-submission estimated that the weighted average cost of NaPb, compounded into either an oral suspension or capsule, was \$█ per gram. This was based on the cost of NaPb powder at \$█ per gram plus compounding costs and mark-ups. The re-submission stated the estimated cost per gram was higher than the price requested in the previous submission of \$█ per gram (at the DPMQ level). Thus the re-submission maintained the proposed price from the previous submission (approved ex-manufacturer price (AEMP) of \$█ per 84g bottle).
- 5.14 As a minor submission, the cost-minimisation analysis was not evaluated. However, the PBAC considered that the analysis was not appropriate because:

- NaBz was not included in the cost-minimisation analysis despite the PBAC previously considering that this would be an appropriate comparator. Further, the re-submission did not estimate the proportion of patients for whom NaBz would be a relevant comparator. The PBAC noted that exclusion of NaBz in the cost-minimisation analysis was not conservative as the November 2017 submission indicated that the price of NaBz tablets was \$ [REDACTED] per gram.
- The PBAC noted that the mark-ups, margins and compounding costs totalled over \$ [REDACTED] for a one-month supply. The PBAC considered that these costs, particularly the [REDACTED]% margin for overheads and profits, were not justified and significantly overestimated the cost of compounded NaPb. In comparison, the PBS compounding fee for extemporaneously prepared benefits is \$9.19. Further, the PBAC considered that the inclusion of mark-ups and margins was not reasonable, as cost-minimisation analyses are generally performed at the AEMP level. Pharmacy mark-ups, overheads and margins are subsequently added to the AEMP using the Administration, Handling and Infrastructure Fee of \$72.43.
- The costings included a significant amount of wastage of raw product ([REDACTED]% wastage for the oral suspension and [REDACTED]% wastage for the capsules). The significant amount of wastage was in part due to the way the monthly quantities were calculated, and may not reflect the level of wastage that would occur in practice. The PBAC considered that this may have further overestimated the cost of compounded NaPb.
- It was not clear whether the excipients and their associated costs were reasonable (\$ [REDACTED] for suspension syrup and \$ [REDACTED] for capsule excipients).
- The cost-offset of formulating coated NaPb into a liquid for patients with a naso-gastric tube was not included.

5.15 The pre-PBAC response acknowledged that the cost-minimisation analysis was conducted at what amounted to 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.

Drug cost/patient /year: \$ [REDACTED]

- 5.16 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 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.
- 5.17 On the other hand, the cost of NaBz tablets (i.e. ready prepared) is \$ [REDACTED]/g. The equi-effective doses were not discussed in the submission so an average cost could not be determined.

Estimated PBS usage & financial implications

5.18 In its previous consideration, the PBAC advised that a re-submission would need to include revised financial estimates. In particular, the PBAC had considered that the previous submission had underestimated market uptake, underestimated the average dose and overestimated cost offsets for hospitalisations (November 2017 PBAC PSD, para 7.9 and 7.11).

5.19 The minor submission revised the utilisation and financial estimates to reflect these and other issues raised in the November 2017 PBAC PSD, as summarised in the table below.

Table 3: Revised inputs to the utilisation and financial estimates

November 2017 PBAC Minutes	How the re-submission addressed it
The prevalent population was overestimated because prevalence rates in adults were assumed to be the same as patients aged under 18 (Para 6.62 a)	Reduced the prevalent population by █% (from the submission estimated █ – reduced to █).
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). (Para 6.62 b)	The identified prevalent pool was assumed to grow in the forward estimates as not all patients have been identified at this point in time. An additional 10% of the prevalent population is assumed to die annually (this in addition to the 30% of early onset patients who die)
The overall share of the total ammonia scavenger market was underestimated (Para 6.62 c)	Given that para. 6.60 suggested the uptake rate is expected to be █% this has been adopted in the first year, rising to █% by year 5.
Doses were based on Kibleur 2014, while doses in the proposed PBS population would likely be higher. (Para 6.62 d)	To make allowance for increased real-world doses, the doses/day was increased by █%.
The estimated hospital cost offsets for displacement of NaPb and NaBz may be different as: <ul style="list-style-type: none"> 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). (Para 6.63) 	<ul style="list-style-type: none"> The revised estimates assume that only █% of patients using NaBz cease using it as a result of the PBS listing of coated NaPb. The uncoated tablets were not offset because it is the Sponsor's understanding that these are not readily available.
Cost offsets for MBS and hospitalisations were significantly overestimated as the rate and costs of hospitalisation for HACs were overestimated. (Para 6.64)	Updated to only include AR-DG P60A (\$█) to cost HAC hospitalisations (PBAC PSD Table 11).
Updated price (the price in the financial estimates was based on the price proposed in November 2017 submission, while a lower price was proposed in the November 2017 Pre-PBAC response).	The AEMP was updated to be \$█, which equates to \$█ DPMQ for 2 bottles.

Source: Table 2, p6 of the minor re-submission

5.20 The revised utilisation and financial estimates presented in the re-submission are outlined in the table below.

Table 4: Updated utilisation and financial estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated	█	█	█	█	█	█
Number of scripts	█	█	█	█	█	█
Net Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
MBS savings	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net Cost to PBS/RBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Hospital Cost Savings	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net Cost to Government	\$█	\$█	\$█	\$█	\$█	\$█
Previous submission						
Number of patients treated	█	█	█	█	█	█
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to government	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 3, p6 of the minor re-submission; Table 12 of the PBAC Minutes, November 2017

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 would be less than \$10 million per year.

- 5.21 The re-submission estimated that the net cost to the PBS/RPBS would be \$30 - \$60 million over six years, compared with \$30 - \$60 million in the previous submission.
- 5.22 As a minor submission, the changes to the financial estimates were not evaluated. However, the PBAC noted that for many of the changes, the magnitude of adjustment was not justified. For example, the prevalent population was reduced by █% and the average dose was increased by █%, but the re-submission did not provide a basis for the values used.

For more detail on PBAC's view, see section 6 PBAC outcome

6 PBAC Outcome

- 6.1 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 cost-minimisation compared with other ammonia scavenger formulations was not adequately established.
- 6.2 The PBAC re-iterated its previous consideration that ammonia scavengers have an important clinical place, and that there is 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.
- 6.3 The PBAC noted that the comparator nominated by the re-submission was uncoated NaPb powder compounded into an oral suspension or capsules by a compounding pharmacy. The PBAC recalled and re-iterated its November 2017 consideration, that

NaBz was also a relevant comparator for a proportion of patients in the monotherapy setting.

- 6.4 The PBAC noted that no new clinical data were provided and re-iterated its previous consideration that a claim of non-inferior comparative efficacy and safety compared with other ammonia scavenger formulations was appropriate given the clinical evidence that had been provided.
- 6.5 Further, the PBAC recalled and re-iterated its November 2017 consideration that a cost-minimisation analysis against other ammonia scavengers would be appropriate.
- 6.6 The PBAC considered that the re-submission's cost-minimisation analysis versus compounded NaPb had significantly overestimated the cost of the comparator because the analysis: excluded NaBz as a comparator; included mark-ups, margins and compounding costs of over \$ [REDACTED] for a one-month supply (including a [REDACTED]% margin for overheads and profits) stating these were based on potential prices in the private market; and did not adequately justify the high level of wastage included. 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.
- 6.7 The PBAC noted that the re-submission had provided revised financial estimates, but considered that, for many of the changes, the magnitude of adjustment was not adequately justified.
- 6.8 The PBAC re-iterated its previous consideration that any re-submission should be a major submission made on a cost-minimisation basis against other ammonia scavengers with revised cost parameters to address the issues raised in Paragraph 5.14. Revised financial estimates would also need to be provided, as outlined in the November 2017 PBAC PSD (Paragraphs 6.62 to 6.64 and 7.9 of the sodium phenylbutyrate November 2017 PBAC PSD).
- 6.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

7 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.

8 Sponsor's Comment

The sponsor had no comment.