

**7.11 SAPROPTERIN,
Tablet (soluble) containing sapropterin dihydrochloride
100 mg,
Kuvan[®],
BioMarin Pharmaceutical Australia.**

1 Purpose of Application

- 1.1 The minor resubmission requested Section 85, Authority required (in writing) listing for sapropterin for the treatment of hyperphenylalaninaemia (HPA) caused by phenylketonuria (PKU). The minor resubmission attempted to address concerns raised in the previous resubmission, which was deferred by the March 2018 PBAC.
- 1.2 The basis for the requested listing remained unchanged and was a cost-utility analysis compared with a strict / relaxed / abandoned phenylalanine (Phe)-restricted diet and Phe-free supplements.

2 Requested listing

- 2.1 The resubmission made the following changes to the requested restriction compared with the previous submission:
 - an initial restriction was proposed seeking PBS-subsidised access to sapropterin for the purposes of initial responsiveness testing. This was to address the DUSC's previous concern that the process for sapropterin responsiveness testing was outside the PBS (Paragraph 2.6, PBAC Public Summary Document (PSD), March 2018 meeting);
 - the definition of initial response was a $\geq 30\%$ reduction in blood Phe levels from baseline in a sapropterin testing period of up to 28 days. The resubmission appropriately excluded the alternative "... or attainment of therapeutic blood Phe goals as defined for an individual patient by the treating physician", which the PBAC previously considered to be broad and subjective (Paragraph 7.6, PBAC PSD, March 2018);
 - a grandfathered restriction was proposed for continuing access for patients who are currently receiving sapropterin; and
 - patients must be under the age of 18 to commence treatment (i.e. sapropterin responsiveness testing must have been undertaken prior to the age of 18 years). Once commenced, the resubmission proposed that patients could continue sapropterin through adulthood. This was to address the PBAC's previous advice that commencement of sapropterin therapy should be restricted to children and adolescents (Paragraph 7.4, PBAC PSD, March 2018).
- 2.2 The restrictions proposed by the minor resubmission are presented below.

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Initial restriction for sapropterin responsiveness testing (as proposed in minor resubmission)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SAPROPTERIN DIHYDROCHLORIDE 100MG, SOLUBLE TABLETS, 30	1*	0	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Kuvan® BioMarin Pharmaceutical Australia Pty Ltd

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity:	Chronic
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Initial
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria	Must be treated by a metabolic physician, medical practitioner or a nurse practitioner, experienced in the treatment of phenylketonuria (PKU)
Clinical criteria:	Patient must have hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Population criteria:	The patient must be under the age of 18 years
Prescriber Instructions:	The authority application must be in writing and include a documented diagnosis of PKU. At the time of authority application, prescribers should request the appropriate number of packs, based on the prescribed dose and weight of the patient, to provide sufficient drug for up to one month of treatment.

* At the time of authority application, prescribers should request the appropriate number of packs, based on the prescribed dose and weight of the patient, to provide sufficient drug for up to one month of treatment.

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Continuing treatment - continuing prescription including grandfathered patients

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SAPROPTERIN DIHYDROCHLORIDE 100MG, SOLUBLE TABLETS, PACK OF 30	1*	5	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Kuvan BioMarin Pharmaceutical Australia Pty Ltd

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity:	Chronic
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Continuing
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria	Must be treated by a metabolic physician, medical practitioner or nurse practitioner, experienced in the treatment of phenylketonuria (PKU)
Clinical criteria:	Patient must have hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) AND Patient must have a demonstrated response to sapropterin AND Patient must have previously been issued with an authority prescription; OR Patient must have accessed non-PBS subsidised treatment prior to [date of listing on the PBS]
Prescriber Instructions:	The authority application must be in writing. For the first authority application for continuing treatment, a documented response to sapropterin must be provided where a response is defined by a $\geq 30\%$ reduction in blood phenylalanine levels from baseline (prior to sapropterin responsiveness testing) in a sapropterin testing period of up to 28 days. Sapropterin responsiveness testing must have been undertaken prior to the age of 18 years. For subsequent authority applications for continuing treatment, documentation of monthly blood test and attendance at 6-monthly visits must be provided. At the time of authority application, prescribers should request the appropriate number of packs, based on the prescribed dose and weight of the patient, to provide sufficient drug for up to one month of treatment. Up to a maximum of 5 repeats will be authorised.

* At the time of authority application, prescribers should request the appropriate number of packs, based on the prescribed dose and weight of the patient, to provide sufficient drug for up to one month of treatment

Blood Phe levels required to be eligible for initial responsiveness testing

2.3 The restriction proposed in the resubmission did not specify the blood Phe levels required to commence sapropterin. There does not appear to be a firm consensus regarding the blood Phe levels at which sapropterin should be commenced, with recommendations varying from $> 360 \mu\text{mol/L}$ to $> 600 \mu\text{mol/L}$, as outlined below. It was also unclear whether different thresholds should be used depending on when the blood

Phe level is measured (e.g. at diagnosis versus prevalent patients on dietary management).

- The Australian guidelines for 'BH4 in the Management of PKU'¹ (sapropterin is a synthetic form of tetrahydrobiopterin (BH4), and the term BH4 also includes other formulations) recommended that patients with Phe blood levels of 600-1200 µmol/L at diagnosis should be tested for sapropterin responsiveness. This was based on the results of a Delphi panel which also found that patients with Phe blood levels ≤ 360 µmol/L at diagnosis do not require treatment, but did not reach consensus regarding whether or not patients with Phe blood levels of 360 to 600 µmol/L should be tested for sapropterin responsiveness.
- On the other hand, the 'Australasian consensus guidelines for the management of phenylketonuria (PKU) throughout the lifespan'² state that "Patients with a blood Phe level above 360µmol/L should be treated as PKU", though this is in the context of dietary treatment rather than sapropterin treatment.
- Correspondence received for the previous submission outlined that in one Australian Centre babies who are diagnosed with PKU with Phe levels > 400 µmol/L at newborn screening are tested for sapropterin responsiveness.
- In the financial estimates, the minor resubmission estimated that the eligible population comprised patients with blood Phe levels > 300 µmol/L, though the resubmission stated this was a proxy for patients with > 360 µmol/L.

2.4 The PBAC considered that, on balance, the PBS restriction should require: newborn patients to have Phe levels > 360 µmol/L at diagnosis; and all other patients to have Phe levels > 600 µmol/L during a stable period of disease.

2.5 The PBAC noted that the ASIEM guidelines for 'BH4 in the management of PKU' state that before conducting initial responsiveness testing, patients/carers should be assessed: for their ability to comply with the sapropterin protocol; expectations of sapropterin; ability to comply with PKU diet; and (for prevalent patients) recent clinic visit history and current dietary Phe tolerance. The guidelines also recommend that for continuing treatment, patients/carers should be "assessed with regards to their compliance and cooperation ... with sapropterin therapy including ability to adhere to ongoing monitoring requirements and dietary recommendations". The PBAC considered that it may be appropriate to incorporate these elements into the PBS restriction.

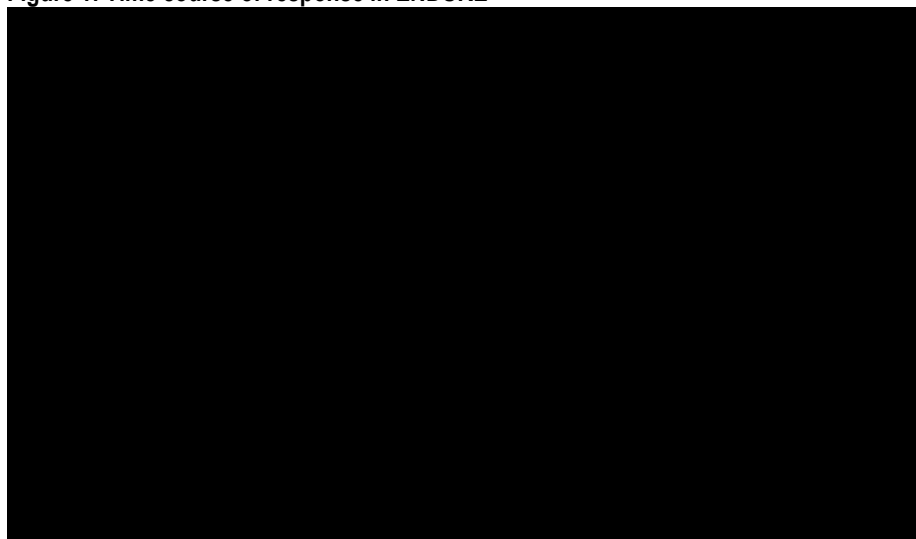
¹ BH4 in the Management of PKU; Australasian Society for Inborn Errors of Metabolism (ASIEM) Clinical Guideline Document. Accessed at: <https://www.hgsa.org.au/documents/item/8655>

² Australasian consensus guidelines for the management of phenylketonuria (PKU) throughout the lifespan. Accessed at: <https://www.hgsa.org.au/documents/item/8664>

Identification of responsive patients: Initial responsiveness testing protocol

- 2.6 The March 2018 PBAC considered that insufficient evidence had been presented for the Committee to be confident that the sapropterin responsiveness test proposed by the resubmission would identify truly responsive patients in terms of correctly identifying patients who are, and patients who are not, responsive. In particular, the PBAC considered that it would be difficult to distinguish true responsiveness from fluctuations in Phe levels due to other causes such as changes in diet or intercurrent illness, particularly given the high underlying variability in Phe levels and the long period of testing that had been proposed (four weeks) (Paragraph 7.7, March 2018 PBAC PSD).
- 2.7 The PBAC considered that these were particular issues in light of the four week initial testing period outlined in the Product Information and proposed in the resubmission (e.g. it is not possible to monitor whether dietary Phe intake is maintained at a constant level during this period, and there may be high intra-patient variability in Phe levels over such a time period). Thus, the PBAC considered that the specificity of a four week initial testing period remained unclear.
- 2.8 The PBAC noted that shorter protocols for initial responsiveness testing had been outlined in guidelines. For example, the Australian guidelines for 'BH4 in the Management of PKU' discuss testing over: a 24 hour period comprising a loading test performed shortly after the results of newborn screening are available; and a 7-day period, incorporating a pre-test Phe load, in patients aged 2-18 years.
- 2.9 The resubmission reported that, across different studies, higher response rates were reported in those studies that used a longer duration of responsiveness testing (28 days duration) compared with those studies that used a shorter duration (7 or 8 days). Further, the resubmission stated that in the ENDURE study, 64% of patients achieved a response at 7 days, with an additional 10% of patients achieving a response between Day 8 and 28. The resubmission also noted that, in ENDURE, response rates fluctuated over the 28 day period, with ■% of patients having achieved a response (i.e. reduction \geq 30% since baseline) at Day 28, although 75% experienced a response at any time within the 28 day period. This is shown in the figure below. This may be indicative of the background fluctuations in blood Phe levels, e.g. due to diet or intercurrent illness.

Figure 1: Time course of response in ENDURE



Source: Figure 1-3, p14 of the minor resubmission

Notes: n = 59 patients for all time points except Day 21 and Day 28 (n = ■)

- 2.10 Given the high intra-patient variability in Phe levels, the PBAC considered that the PBS restriction should require a 24-hour testing period in newborns and a 7-day testing period in children and adolescents. The PBAC noted that the shorter responsiveness testing periods may reduce the number of people who achieve a response (as shown Figure 1), but in the absence of a more robust method for identifying patients who are truly responsive, this would provide greater certainty that those patients accessing sapropterin under the PBS are “truly responsive”. The PBAC considered this was necessary to provide increased confidence as to the incremental effectiveness that would be achieved in clinical practice.

Identification of responsive patients: Assessment of initial response and basis for threshold of $\geq 30\%$ reduction in blood Phe levels

- 2.11 The minor resubmission proposed that response to sapropterin would be defined as a $\geq 30\%$ reduction in blood Phe levels from baseline (prior to sapropterin responsiveness testing) in a sapropterin testing period of up to 28 days.
- 2.12 Compared with the previous submission, the definition of responsiveness proposed in the resubmission appropriately removed a subjective assessment of “...attainment of the therapeutic blood phenylalanine goals defined for an individual patient ...” (in line with Paragraph 7.6 of the March 2018 PBAC PSD).
- 2.13 The March 2018 PBAC had requested additional information as to the underlying basis for the use of a target threshold of a 30% reduction in Phe levels and whether the 30% reduction was relevant regardless of baseline Phe levels (Paragraph 2.5, March 2018 PBAC PSD). The minor resubmission stated that the basis was historical with no rationale provided in early publications, but that this threshold has been accepted in studies and guidelines. For example, the Australian and European guidelines state that a target of 30% reduction in blood Phe appears to be an adequate compromise between sensitivity

and specificity, though the Australian guidelines acknowledge that this target is arbitrary. Further, the Australian guidelines for 'BH4 in the Management of PKU' reported that there was a 95% agreement in a Delphi survey of Australasian PKU experts that a $\geq 30\%$ reduction in blood Phe levels was a clinically significant response to BH4 therapy.

- 2.14 The PBAC considered that a $\geq 30\%$ reduction in blood Phe levels is consistent with the guidelines and clinical data presented in the previous submission, and represents a reasonable balance between sensitivity and specificity.

Assessment of continuing response

- 2.15 The previous submission proposed that evidence of sustained benefit would need to be provided every six months for continuing access. That is, the proposed continuing restriction had previously included the instruction that "the authority application must ... include documentation of blood Phe levels within the target range, or a maintenance of blood Phe levels achieved at sapropterin responsiveness testing".
- 2.16 However, the minor resubmission's proposed continuing restriction was less stringent in terms of assessing continuing response, stating "For subsequent authority applications for continuing treatment, documentation of monthly blood test and attendance at 6-monthly visits must be provided". The proposed restriction did not specify particular levels at which blood Phe should be maintained in order to demonstrate a continuing response.
- 2.17 The PBAC noted that there do not appear to be any guidelines that specify particular levels at which blood Phe should be maintained for continued access to sapropterin. The PBAC considered that any continuation requirements based on Phe levels would potentially be confounded by intra-patient variability. Thus, the PBAC considered that the risk of use in patients not continuing to respond would be better managed through a Risk Sharing Arrangement, rather than PBS restriction criteria.
- 2.18 For continuing treatment, the Australian guidelines for 'BH4 in the Management of PKU' specify that blood monitoring should occur at the same frequency as the other patients with PKU, and that patients/carers should be "assessed with regards to their compliance and cooperation ... with sapropterin therapy including ability to adhere to ongoing monitoring requirements and dietary recommendations" and that "long-term supplementation and ongoing evaluation are required to demonstrate true responsiveness".
- 2.19 The PBAC considered that regular routine follow-up was necessary to ensure that sapropterin is not used as a replacement to diet, and that a requirement around this should be included in the PBS restriction. The PBAC acknowledged that the degree of follow-up depends on patient age and disease severity, but considered that a requirement for regular blood tests and 6-monthly visits was reasonable.

Age: Continuation once patients turn 18

- 2.20 In its previous consideration, the PBAC “considered that commencement of sapropterin therapy should be restricted to children and adolescents” (Paragraph 7.4, March 2018 PBAC PSD). The proposed restriction would allow continuation once a person turns 18 years of age, provided they had commenced sapropterin prior to the age of 18.
- 2.21 The minor resubmission provided correspondence from the Metabolic Dietary Disorders Association (MDDA), who considered that continuity of sapropterin treatment for paediatric patients after they turn 18 years of age was critical and stated that without certainty of ongoing access to sapropterin treatment, the MDDA would discourage parents and patients from commencing sapropterin treatment. It stated that patients treated with sapropterin may not be able to adhere to the strict Phe-restricted diet necessary to maintain blood Phe levels in the therapeutic range without sapropterin. Further, it stated that managing a strict Phe-restricted diet is especially challenging during adolescence and adulthood when parental control over diet diminishes, and while lifestyle changes occur such as transitioning to secondary to tertiary education, independent living, and commencing work. The MDDA also stated that patients are vulnerable to poor management or becoming lost to treatment at 18 years of age when they transition from paediatric to adult health services.
- 2.22 The PBAC recalled that it had previously considered that the benefits of sapropterin in terms of improved neurological function were likely to be greatest during the development period for children and adolescents, and that the cost-effectiveness was likely more favourable in children compared with those aged ≥ 18 years. The PBAC noted that the pre-PBAC response had proposed a mechanism that may help improve the cost-effectiveness and reduce the financial impact of continuing patients aged ≥ 18 years (discussed in ‘Estimated PBS usage & financial implications’ below).
- 2.23 In light of the revised RSA proposal and the risks of ceasing treatment once commenced, the PBAC considered that it would be appropriate to allow patients who commenced PBS-subsidised sapropterin prior to the age of 18 years to continue thereafter.
- 2.24 The PBAC noted that the financial estimates did not include grandfathering of patients aged over 18 (i.e. the resubmission assumed that only patients under the age of 18 would be eligible to access PBS-subsidised sapropterin through the grandfathering restriction) and considered this was appropriate and consistent with its recommendation that only patients who commenced PBS-subsidised sapropterin prior to the age of 18 years could continue thereafter.

Grandfathering restriction

- 2.25 The resubmission proposed a combined restriction for continuing therapy and grandfathered patients. However, the Secretariat has proposed a separate restriction for grandfathered patients given such patients would be required to have previously met the initial criteria (i.e. blood Phe levels above a particular threshold and that sapropterin therapy must have been commenced when the patient was under the age of 18 years).
- 2.26 The resubmission proposed that grandfathered patients would not need to re-demonstrate sapropterin responsiveness, irrespective of when response testing was conducted.

Other issues

- 2.27 The proposed initial and continuing restrictions both state that the patient “Must be treated by a metabolic physician, medical practitioner or a nurse practitioner, experienced in the treatment of phenylketonuria (PKU)”. The pre-PBAC response stated that patients with PKU are managed predominantly by nurse practitioners at metabolic clinics, and that general practitioners do not manage PKU. As such, the PBAC considered that the restriction should allow prescribing by metabolic physicians or nurse practitioners experienced in the treatment of PKU.
- 2.28 The minor resubmission proposed that both the initial and continuing restrictions be Authority Required – In Writing.
- 2.29 The requested restriction is considered to be complex given the need for criteria for assessing initial and continuing response.

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

3 Background

- 3.1 Sapropterin was TGA registered on 21 October 2010 for “the treatment of HPA in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency”.
- 3.2 The PBAC has considered sapropterin for the treatment of PKU twice previously:
- The first submission (requesting listing for both PKU and BH4 deficiency) was considered at the November 2011 PBAC meeting.
 - A resubmission was considered in March 2018 at which the PBAC deferred making a decision.
- 3.3 Relevant details compared with the March 2018 resubmission are provided in the table below.

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Table 1: Summary of the March 2018 submission and the current resubmission

	March 2018 submission	Current resubmission
Requested PBS listing	<ul style="list-style-type: none"> No age criteria were proposed. Sponsor would provide access to sapropterin for the purpose of sapropterin responsiveness testing. Initial responsiveness based on either a $\geq 30\%$ reduction in blood Phe levels or attainment of therapeutic blood Phe goals as defined for an individual patient. Continuing response: evidence of sustained benefit would need to be provided every six months (documentation of Phe levels within the target range, or maintenance of Phe levels achieved at sapropterin responsiveness testing). No grandfathering arrangements proposed. <p>The PBAC considered the greatest benefits would be experienced in children and adolescents (Para 7.1) and noted a number of issues with the proposed restrictions, such as accessing sapropterin for the purpose of responsiveness testing, grandfathering requirements, auditing requirements and assessing continuing response (Para 7.8).</p>	<ul style="list-style-type: none"> Patients must be aged < 18 years to commence, and can continue through adulthood. An initial restriction was proposed seeking PBS-subsidised access to sapropterin for the purposes of initial responsiveness testing. Initial responsiveness based only on a $\geq 30\%$ reduction in blood Phe levels. Continuing response: documentation of monthly blood test and attendance at 6-monthly visits must be provided A grandfathered restriction was proposed.
Requested effective DPMQ	\$ [REDACTED]	Unchanged
Comparator	<ul style="list-style-type: none"> Placebo + a relaxed or abandoned diet' for individuals with poorly-controlled blood Phe-levels; and 'A strict Phe-restricted diet' for those with well-controlled blood Phe levels. <p>The PBAC considered this was not informative because these were not two distinct sub-populations (Para 7.9).</p>	Unchanged
Key effectiveness data	<ul style="list-style-type: none"> Response to sapropterin ($\geq 30\%$ reduction in Phe levels) ranged from 20% (PKU-001) to 75% (ENDURE). <p><u>Among patients not adhering to a strict diet:</u></p> <ul style="list-style-type: none"> a 245 $\mu\text{mol/L}$ reduction in blood Phe levels over a 6 week duration (PKU-003). <p><u>Among patients who were adhering to a strict diet:</u></p> <ul style="list-style-type: none"> a 17.7 mg increase in Phe tolerance over 6 weeks; a 30.5 mg increase in Phe tolerance over 26 weeks. 	Unchanged
Clinical claim	Superior comparative effectiveness and non-inferior comparative safety versus either a relaxed or strict Phe-restricted diet. The PBAC considered these claims were reasonable (Para 7.10 and 7.11).	Unchanged

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	March 2018 submission	Current resubmission
Economic evaluation	<p>Cost-effectiveness analysis against: 'placebo + a relaxed or abandoned diet' for individuals with poorly-controlled blood Phe-levels; 'a strict Phe-restricted diet' for those with well-controlled blood Phe levels.</p> <ul style="list-style-type: none"> Separate ICERs were calculated for each of the subpopulations; these were combined in a weighted analysis for the base-case economic evaluation. ICERs for each age between 0 and 17 years and one for ≥ 18 years, with a one year time horizon for each age group. The ICER ranged from \$ [redacted] /QALY for patients aged < 1 year to \$ [redacted] /QALY for those aged 16 years. <p>"The PBAC considered that the resulting ICER for patients aged 18 years and over... was unacceptably high. The PBAC noted the ICERs for patients under 18 years of age were generally lower... While the PBAC considered that the ICERs were high in children and adolescents, the Committee considered that the clinically significant outcomes in younger patients may not have been fully captured in the economic evaluation (Para 7.13).</p>	<ul style="list-style-type: none"> The DPMQ of Phe-free amino acid supplements (PKU Cooler) was updated. The annual cost of sapropterin was updated to remove rounding. The ICER ranged from \$ [redacted] /QALY for patients aged less than one year to \$ [redacted] /QALY for those aged 17 years. <p>Calculated a single weighted average ICER (taking account of the revised age criteria) across all age groups for each individual year of listing for the 6-year period from 2019 to 2024. The average ICER over the 6 years was \$ [redacted] /QALY.</p>
Number of patients	<p>[redacted] in Year 1, increasing to [redacted] in Year 6 (maintenance only).</p>	<p>[redacted] in Year 1, increasing to [redacted] in Year 6 (maintenance only), reduced in the pre-PBAC response to [redacted] in Year 1 and [redacted] in Year 6.</p> <p>Higher in Year 1 due to higher uptake rate, lower in Year 6 due to exclusion of patients aged ≥ 18 years (except for continuing use).</p>
Estimated net cost to PBS	<p>\$ [redacted] million in Year 6 and \$ [redacted] million over the first six years (cost of sapropterin only, for comparison). The PBAC considered that the financial estimates would need to be updated: to reflect commencement in children and adolescents only; the eligible population may be overestimated due to inconsistencies between the clinical guidelines and the criteria used to determine the eligible population; the uptake and compliance rates were underestimated; and the rounding of doses was inappropriate (Para 7.16).</p>	<p>\$ [redacted] million in Year 6 and \$ [redacted] million over 6 years. Reduced in the pre-PBAC response to \$ [redacted] million in Year 6 and \$ [redacted] million over 6 years. Cost over 6 years was much lower than estimated in the previous submission due to patients aged ≥ 18 years no longer being eligible to commence sapropterin.</p>
Key changes to financial estimates	<ul style="list-style-type: none"> offsets for reductions in use of Phe-free amino acid supplements were estimated to be \$ [redacted] million over six years. Included incident and prevalent patients aged 0 to 51 years. % respond to initial sapropterin responsiveness testing: [redacted]% in well controlled patients and [redacted]% in poorly controlled patients. Uptake rate: [redacted]% in Year 1 increasing to [redacted]% in Year 6 in children and adolescents; and [redacted]% in Year 1 increasing to [redacted]% in Year 6 in patients aged ≥ 18 years. Dose of sapropterin rounded to nearest 100mg. Compliance rate: 100%. 	<ul style="list-style-type: none"> No offsets for reductions in use of Phe-free amino acid supplements were included. Included patients aged 0 to 17 years and assumed patients can continue once they turn 18 years. % respond to initial sapropterin responsiveness testing: [redacted]% across all patients. Uptake rate: [redacted]% (in all years and all patient ages), amended to [redacted]% in pre-PBAC response. Dose of sapropterin not rounded. Compliance rate: [redacted]%, amended to [redacted]% in pre-PBAC response.

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	March 2018 submission	Current resubmission
Risk sharing arrangement	<ul style="list-style-type: none"> Commonwealth expenditure would be capped at the estimates provided with a [REDACTED]% rebate for above this level. The PBAC considered that an RSA would be required to manage the high and uncertain cost-effectiveness and the uncertain patient population. The PBAC considered that the RSA should include 100% rebates for expenditure beyond the cap. (Para 7.14) 	<ul style="list-style-type: none"> Commonwealth expenditure would be capped at the estimates provided with a [REDACTED]% rebate for above this level. [REDACTED]% rebate on the cost to the PBS of all sapropterin used for initial responsiveness testing. Pre-PBAC response also proposed a rebate for patients ≥18 years
PBAC decision	<p>Defer.</p> <p>PBAC Comment: The PBAC sought further evidence regarding processes for determining whether or not a patient is responsive to sapropterin and the patient population in which treatment would result in the greatest benefit, in terms of clinically significant outcomes such as cognitive function and supporting growth. The PBAC considered the greatest benefits would be experienced in children and adolescents. (Para 7.1)</p>	-

Source: Compiled during the preparation of the Minor Overview. Paragraph references for March 2018 refer to the sapropterin public summary document.

ICER = incremental cost effectiveness ratio

4 Comparator

4.1 The minor resubmission did not nominate a comparator. However, for the purposes of the economic model, the nominated comparators were unchanged from the previous submission and were:

- ‘placebo + a relaxed or abandoned diet’ for individuals with poorly-controlled blood Phe-levels; and
- ‘a strict Phe-restricted diet’ for those with well-controlled blood Phe levels.

4.2 In its previous consideration, the PBAC considered that the approach of splitting the patient population into those with poorly-controlled and those with well-controlled blood Phe levels (for the purpose of nominating differential comparators, outcomes and economic models) was not informative because these were not two distinct sub-populations (Paragraph 7.9, March 2018 PBAC PSD).

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 individuals (6) and an organisation (the MDDA) via the Consumer Comments facility on the PBS website. The comments described the impact of PKU on patient quality of life including on mental health.

5.3 The MDDA acknowledged the significant clinical benefit that maintaining low blood Phe levels represents in children and adolescents. The MDDA also considered that the clinical benefits in adults are less researched but that emerging research indicates that

lower blood Phe levels throughout life may have a positive impact on mental health, executive function, concentration and psychosocial functioning.

Clinical trials

- 5.4 The PBAC previously considered that the claims of superior comparative effectiveness and non-inferior comparative safety versus a Phe-restricted diet (relaxed or strict diet) were reasonable (Paragraph 7.10 and 7.11, March 2018 PBAC PSD).

Economic analysis

- 5.5 Like the previous submission, the minor resubmission presented a cost-effectiveness analysis against: 'placebo + a relaxed or abandoned diet' for individuals with poorly-controlled blood Phe-levels; and 'a strict Phe-restricted diet' for those with well-controlled blood Phe levels.
- 5.6 The minor resubmission did not alter the economic model structure but the following minor updates were made:
- The DPMQ of Phe-free amino acid supplements (PKU Cooler) was updated: to incorporate price reductions that took effect from 1 June 2018 (reduced from \$0.81 per mg to \$0.70 per mg). This was appropriate.
 - The annual cost of sapropterin was updated to remove rounding, in line with the PBAC's previous advice (paragraph 7.16, March 2018 PBAC PSD). The previous submission had calculated the average cost of sapropterin by rounding the mean weighted dosage (█████ mg/kg/day multiplied by the average weight for that age group) for each age group to the nearest 100 mg/day. The February 2018 DUSC advice considered this was inappropriate because it may over or underestimate the annual number of prescriptions. While this method would have been appropriate for calculating doses on an individual patient basis (per the Product Information), applying this rounding to all patients in each age group systematically over or underestimates the annual number of sapropterin patients. This amendment was appropriate, and resulted in the average dose of sapropterin being higher in some age groups but lower in others.
- 5.7 Unchanged from the previous submission, separate incremental cost effectiveness ratios (ICERs) were calculated for each of the subpopulations (the 'poorly-controlled Phe level' group and the 'well-controlled Phe level' group). These were combined in a weighted analysis for the base-case economic evaluation.
- 5.8 Also unchanged from the previous submission, the minor resubmission calculated ICERs for each age between 0 and 17 years and one for ≥ 18 years, with a one year time horizon for each age group. The resulting weighted ICERs for each age group are presented in the table below.

Table 2: Results of the economic evaluation – weighted analysis of the poorly- and well-controlled groups

Age	% in well controlled Phe group	Current resubmission						Weighted ICER (\$/QALY)	Previous submission Weighted ICER
		Poorly controlled Phe level group			Well controlled Phe level group				
		Δ Costs	Δ Outcomes	ICER (\$/QALY)	Δ Costs	Δ Outcomes	ICER (\$/QALY)		
0	82%	\$		\$		\$		\$	
1	82%	\$		\$		\$		\$	
2	82%	\$		\$		\$		\$	
3	82%	\$		\$		\$		\$	
4	82%	\$		\$		\$		\$	
5	82%	\$		\$		\$		\$	
6	82%	\$		\$		\$		\$	
7	82%	\$		\$		\$		\$	
8	82%	\$		\$		\$		\$	
9	82%	\$		\$		\$		\$	
10	82%	\$		\$		\$		\$	
11	82%	\$		\$		\$		\$	
12	82%	\$		\$		\$		\$	
13	85%	\$		\$		\$		\$	
14	85%	\$		\$		\$		\$	
15	85%	\$		\$		\$		\$	
16	85%	\$		\$		\$		\$	
17	85%	\$		\$		\$		\$	
≥18	35%	\$		\$		\$		\$	

Source: 'economic evaluation' worksheet

^a Weighted QALYs were based on weighting between the 'poorly-controlled Phe level' group and the 'well-controlled Phe level' group. The submission estimated that incremental QALYs are higher in patients aged ≥18 because more patients were assumed to be in the poorly controlled group (65% of patients aged ≥18 were assumed to be poorly controlled, versus 15% in those aged <18 years), where incremental QALY gains were estimated to be higher. This may not be appropriate the PBAC previously considered that the clinically significant outcomes in younger patients may not have been fully captured in the economic evaluation (Para 7.13, March 2018 PSD).

The redacted table shows ICERs in the range of \$45,000/QALY – more than \$200,000/QALY.

- 5.9 The ICER ranged from \$45,000/QALY - \$75,000/QALY for patients aged less than one year to more than \$200,000/QALY for those aged 17 years. Compared with the previous submission, the ICER was higher in some age groups but lower in others (as the effect of rounding the dose differed by age group). The PBAC noted that the ICER for patients aged ≥ 18 years would substantially reduce with the RSA arrangements proposed in the pre-PBAC response (outlined in 'Estimated PBS usage & financial implications') if utilisation was at or above the levels estimated in the pre-PBAC response.
- 5.10 As noted in the previous Minutes, the ICER generally increased with age (from 0 to 17 years) because the dose of sapropterin is weight-based. The ICER decreased after 17 years of age because the proportion of patients assumed to be poorly controlled increased from 15% to 65%. Sapropterin was estimated to be more cost-effective among the 'poorly-controlled' sub-population, mainly because lower quality-adjusted life years (QALYs) were accrued in the 'poorly-controlled' comparator arm (utility value between [redacted] and [redacted], depending on age) compared with the 'well-controlled' comparator arm (utility of [redacted]), while the drug cost of sapropterin was the same in the two sub-populations.
- 5.11 The resubmission calculated a single weighted average ICER across all age groups for each year of listing, using the estimated number of patients in each age group (from the

financial estimates). This was conducted for each year of listing from 2019 to 2024. The ICER increased over the six-year period because the proportion of patients aged 18 years and over was estimated to gradually increase. Using this method, the ICER per QALY increased from more than \$200,000 in Year 1 of listing to more than \$200,000 in Year 6. The average ICER over the six years was estimated to be more than \$200,000 per QALY.

- 5.12 During preparation of the minor overview, the ICER was also calculated for a patient who commences sapropterin at birth and continues until either their 18th or 40th birthday (shown in the table below). The economic evaluation assumed that patients would have full compliance. Compliance may be lower in clinical practice, which would impact both the costs and outcomes. The PBAC also noted that the ICER for a patient who commences at age 0 and continues until their 40th birthday would reduce with the RSA arrangements proposed in the pre-PBAC response.

Table 3: Results of the economic evaluation - weighted ICER for a patient who commences sapropterin at birth

Poorly controlled Phe level group			Well controlled Phe level group			Weighted ICER (\$/QALY)
Incremental Costs	Incremental Outcomes	ICER (\$/QALY)	Incremental Costs	Incremental Outcomes	ICER (\$/QALY)	
ICER for patient who commences at age 0 and continues until 18th birthday (18 year time horizon)						
\$		\$	\$		\$	\$
ICER for patient who commences at age 0 and continues until 40th birthday (40 year time horizon)						
\$		\$	\$		\$	\$

Calculated from 'Attachment 4- Kuvan (sapropterin) – Economic Evaluation.xlsx' by:

- A discount rate of 5% was applied to incremental costs and also to incremental outcomes at each year of age (using sumproduct formula);
- A half-cycle correction was not applied, as all patients were assumed to start at birth; and
- Compliance was assumed to remain constant (█% compliance at an average dose of █ mg/kg/day) over the time horizon.
- Based on the price proposed in the resubmission. The rebate for patients aged ≥ 18 years (proposed in the pre-PBAC response) would lower the ICER for the scenario in which a patient continues until their 40th birthday if utilisation is at or above the levels estimated in the pre-PBAC response.

The redacted table shows ICERs in the range of \$105,000/QALY - more than \$200,000/QALY.

- 5.13 In its previous consideration, “the PBAC considered that the resulting ICER for patients aged 18 years and over... was unacceptably high. The PBAC noted the ICERs for patients under 18 years of age were generally lower... While the PBAC considered that the ICERs were high in children and adolescents, the Committee considered that the clinically significant outcomes in younger patients may not have been fully captured in the economic evaluation” (Paragraph 7.13, March 2018 PBAC PSD).

Drug cost/patient /year

- 5.14 The cost of sapropterin per patient per year ranged from \$█ in the newborn cohort to \$█ in the ≥ 18 year-old cohort. These costs were determined by applying the proposed effective sapropterin DPMQ (\$█) to mean weight-by-age data and a mean daily dose of █ mg/kg/day (derived from study evidence), and assuming █% compliance (per the updated financial estimates provided in the pre-PBAC response).

- 5.15 The pre-PBAC response proposed a rebate for continuing patients aged ≥ 18 years, such that the estimated price for a patient aged ≥ 18 years █.

Estimated PBS usage & financial implications

- 5.16 The resubmission made several changes to financial estimates.
- 5.17 Firstly, sapropterin doses for the initial period of responsiveness testing (up to one month) were included in the estimates, whereas in the previous submission these doses were proposed to be provided by the sponsor. This change was appropriate and addressed previous concerns that the process for sapropterin responsiveness testing was outside the PBS (Paragraph 2.6, PBAC PSD March 2018). The minor resubmission proposed that ■■■% of the cost to the PBS for responsiveness testing would be rebated. The minor resubmission assumed that all eligible patients would undergo responsiveness testing, and assumed that:
- 100% of all prevalent patients in Year 1 would undergo responsiveness testing. The minor resubmission stated that this was likely overestimated because a proportion of patients would already have been tested (i.e. these patients may access sapropterin through the grandfathered listing if aged 0 to 17 years).
 - In Years 2 to 6, only patients aged 0 years would undergo response testing.
 - Patients would require a dose of ■■■ mg/kg per day for a 28 day response testing period. The PBAC noted this may need to be adjusted for the shorter response testing periods outlined in the recommended restriction (24 hours for newborns and 7 days for older children and adolescents).
 - Overall, these assumptions were likely conservative in the context of the proposed ■■■% rebate on all doses dispensed for responsiveness testing.
- 5.18 Further, the resubmission assumed that all patients who undergo sapropterin responsiveness testing would require an additional specialist visit (MBS item 105, a fee of \$43.00 was assumed, rather than the 85% benefit of \$37.15).
- 5.19 Other changes to the financial estimates included:
- The patient population was no longer split into well-controlled and poorly-controlled groups, which had previously been used to estimate offsets for reductions in use of Phe-free amino acid supplements, and also for applying differential uptake rates between the two groups.
 - Offsets were not included for reductions in use of PBS-subsidised Phe-free amino acid supplements. The rationale for this was not clear. In the previous submission, PBS offsets for dietary supplements were estimated to be less than \$10 million over six years.
 - Utilisation was updated to reflect the assumption that the patient population are those aged 0 to 17 years as well as those who continue PBS-subsidised sapropterin once they turn 18 years of age. Thus, the resubmission excluded prevalent patients aged 18 and over. This significantly reduced the eligible population: In the previous submission, ■■■% of patients were aged 18 and over (over the first six years of listing), versus ■■■% in the minor resubmission.
 - The resubmission estimated that ■■■% of patients would respond to initial sapropterin responsiveness testing (whereas the previous submission had assumed

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response rates of █% in well controlled patients and █% in poorly controlled patients). The resubmission stated that initial response rates were between █% and █%, which appeared to be based on studies using responsiveness testing protocols with durations between 24 hours and 28 days. Thus the resubmission used the midpoint of █%. As outlined in ‘Requested listing’, the PBAC considered that 24-hour or 7-day responsiveness testing periods (depending on age) were required in order to provide greater certainty that those patients accessing sapropterin are “truly responsive”. The PBAC noted that the evidence presented in the resubmission showed that █% of patients were responsive in studies using a 24 hour testing period, and █% were responsive using a 7-day testing period. Thus, while it may be expected that shorter responsiveness testing periods may reduce the proportion of people who respond, the PBAC considered that it was appropriate to use a █% response rate in the financial estimates. This was because the █% response rate already included studies with shorter durations of responsiveness testing, and aligned with the midpoint between the response rates observed in studies that used 24-hour and 7-day testing. While acknowledging this was likely the best available data, the PBAC considered the estimate remained uncertain given the heterogeneity between these studies (in terms of sapropterin dose and the patient population) and potential lack of applicability to the PBS population, in the context of financial estimates that are highly sensitive to this parameter.

- An uptake rate of █% was assumed in all years. This was to address the PBAC’s previous concern that the uptake rates were underestimated (Paragraph 7.13, March 2018 PBAC PSD). The uptake rates in the previous submission (among responsive patients) were assumed to be █% in Year 1 increasing to █% in Year 6 in children and adolescents; and █% in Year 1 increasing to █% in Year 6 in patients aged ≥ 18 years. The Minor Overview considered that the markedly higher uptake rate used in the minor resubmission (90%) likely overestimated the treated population. To address this, the pre-PBAC response updated the uptake rate from █% to █%.
- The dose of sapropterin was appropriately not rounded, per the economic analysis.
- A compliance rate of █% was assumed in the maintenance phase (i.e. outside initial responsiveness testing), based on study PKU-008. This was to address the DUSC’s previous concern that a ‘100% compliance rate may not reflect a real-world situation’ (Paragraph 6.67, PBAC PSD March 2018). The Minor Overview considered that compliance likely remained overestimated. To address this, the pre-PBAC response updated the compliance rate from █% to █%.

- 5.20 Unchanged from the previous submission, the eligible population remained based on patients with blood Phe levels ≥ 300 µmol/litre, rather than ≥ 360 µmol/litre (thus, the proportion of patients estimated to be eligible for treatment remained at █%). The DUSC previously considered that this overestimated the eligible population, and thus the Minor Overview considered that the eligible population likely remained overestimated. To address this, the pre-PBAC response updated the eligible population from █% to █%.

- 5.21 The resubmission proposed that patients who commence sapropterin under the age of 18 years be allowed to continue into adulthood, but the Minor Overview noted that the sponsor had not proposed any mechanisms to improve the cost-effectiveness or reduce the financial impact in older patients. This was despite the benefits of sapropterin (in terms of improved neurological function) likely being lower in adults, and both the ICER and cost per patient being significantly higher in adults. To address these uncertainties, the pre-PBAC response proposed an RSA rebate such that the cost of sapropterin for patients aged ≥ 18 years is estimated [REDACTED]. The PBAC noted this would lower the financial impacts and may improve the cost-effectiveness in patients who continue sapropterin past the age of 18 years.
- 5.22 Table 4 summarises the estimated use and financial implications provided in the pre-PBAC response (with the following changes as outlined above: reduced the eligible population from [REDACTED]% to [REDACTED]%; reduced uptake from [REDACTED]% to [REDACTED]%; reduced compliance from [REDACTED]% to [REDACTED]%; and included a rebate for patients aged ≥ 18 years).

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Table 4: Estimated use and financial implications of listing sapropterin – as proposed in pre-PBAC response ^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
No. patients - initial testing						
No. scripts - initial testing						
No. patients - maintenance						
No. scripts - maintenance						
Total no. scripts dispensed						
Estimated financial implications of sapropterin at effective price						
Cost to PBS less co-payments	\$	\$	\$	\$	\$	\$
Rebates proposed in pre-PBAC response						
Rebate for patients ≥18 years	\$	-\$	-\$	-\$	-\$	-\$
Rebate for responsiveness testing	-\$	-\$	-\$	-\$	-\$	-\$
Net cost of sapropterin including both rebates						
Net cost to PBS (RSA cap)	\$	\$	\$	\$	\$	\$
Cost to MBS	\$	\$	\$	\$	\$	\$
Net cost to PBS/MBS	\$	\$	\$	\$	\$	\$
November 2018 resubmission (before changes proposed in pre-PBAC response)						
Net cost to PBS	\$	\$	\$	\$	\$	\$
Previous submission (March 2018)						
Net cost to PBS	\$	\$	\$	\$	\$	\$

Source: Table 1, p3 of the pre-PBAC response

^a Net PBS costs in this table do not include the impact of any offsets from reduced use of PBS-subsidised Phe-free amino acid supplements.

The redacted table shows that at Year 6 the estimated number of total scripts dispensed was less than 10,000 per year.

5.23 The pre-PBAC response estimated that the net cost to the PBS would be less than \$10 million in Year 6 and \$30 - \$60 million over the first six years of listing. This included the impact of the sponsor rebating:

- % of the cost of doses used for initial responsiveness testing. This was estimated to be less than \$10 million over the first six years based on the 28 day responsiveness testing period assumed in the resubmission. The PBAC noted this may need to be updated for the shorter responsiveness testing periods recommended in the restriction; and
- the difference between the estimated price for patients aged ≥ 18 years and . This was estimated to result in a rebate of over the first six years.

5.24 The PBAC noted that the estimated cost to the PBS of listing sapropterin had substantially reduced since the previous submission (the March 2018 submission estimated a cost to the PBS of more than \$100 million over six years), with most of the reduction due to patients aged ≥ 18 years no longer being eligible to commence sapropterin. The PBAC also noted that the updated parameters provided in the pre-

PBAC response further substantially reduced the estimated cost to the PBS (from \$30 - \$60 million over six years in the November 2018 submission to \$30 - \$60 million in the pre-PBAC response).

Financial Management – Risk Sharing Arrangements

- 5.25 In its previous consideration, the PBAC stated that a risk sharing arrangement (RSA) would be required to manage the high and uncertain cost-effectiveness and the uncertain patient population, and that a resubmission would need to provide a revised RSA based on updated financial estimates (Paragraphs 7.14 and 7.17, PSD March 2018). The minor re-submission and pre-PBAC response proposed an RSA where PBS/RPBS expenditure would be capped at the estimates provided in Table 4 (based on the “Net cost to PBS (RSA cap)” row) with a [REDACTED] % rebate to PBS/RPBS expenditure above this level.
- 5.26 As outlined above, the proposed expenditure cap also included a rebate for patients aged ≥ 18 years and a [REDACTED] % rebate on the cost to the PBS of all sapropterin used for initial responsiveness testing.
- 5.27 The resubmission proposed that the rebate for initial responsiveness testing would be administered as a separate rebate based on actual utilisation of the corresponding PBS item once listed, as a separate listing has been proposed for responsiveness testing.

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

6 PBAC Outcome

- 6.1 The PBAC recommended extending the PBS-listing of sapropterin to include the treatment of hyperphenylalaninaemia (HPA) caused by phenylketonuria (PKU) as a Section 85 Authority Required listing. The PBAC was satisfied that sapropterin provides, for some patients, a significant improvement in efficacy over a Phe-restricted diet alone. In making this recommendation, the PBAC noted there was a high clinical need in a small patient population, and acknowledged the input received from individuals, organisations and health professionals. The PBAC considered that an RSA would be required to manage the high and uncertain cost-effectiveness, the uncertain patient population, and the risk of use in patients not continuing to respond.
- 6.2 The PBAC considered that the greatest clinical benefits would be achieved in children and adolescents and thus reiterated its previous consideration that sapropterin should only be commenced in patients who are younger than 18 years of age.
- 6.3 The PBAC considered that patients who commenced PBS-subsidised sapropterin prior to the age of 18 years should be allowed to continue sapropterin thereafter. The PBAC noted correspondence from the MDDA who advised that patients previously treated with sapropterin may not be able to adhere to the stricter Phe-restricted diet that would be required if sapropterin were ceased once a patient reached adulthood. The PBAC considered that the RSA proposal (outlined further below) would address some of its concerns about the cost-effectiveness and financial impacts for continuing patients aged 18 years and over, given the risks associated with these patients ceasing

sapropterin after have been stabilised on treatment.

- 6.4 The PBAC considered that the initial PBS restriction should require:
- newborn patients to have Phe levels > 360 µmol/L at diagnosis, and all other patients to have Phe levels > 600 µmol/L during a stable period of disease.
 - assessment of patients/carers for their ability to comply with the sapropterin protocol, expectations of sapropterin, ability to comply with PKU diet and, for prevalent patients, recent clinic visit history and current dietary Phe tolerance.
- 6.5 Further, the PBAC considered that the PBS restriction should require that initial sapropterin responsiveness testing be conducted over a 24-hour period in newborns and a 7-day period in children and adolescents. The PBAC considered this would help address its previous concerns that it would be difficult to distinguish true responsiveness from fluctuations in Phe levels due to other causes such as changes in diet or intercurrent illness, particularly given the high underlying variability in Phe levels which may be more marked over a 4-week period. The PBAC noted that guidelines had outlined initial responsiveness testing periods of 24-hours in newborns and 7-days in children and adolescents. The PBAC considered these shorter testing periods were necessary to provide greater certainty that patients accessing sapropterin are truly responsive and would provide increased confidence around the incremental effectiveness that would be achieved in clinical practice.
- 6.6 The PBAC considered that response to sapropterin during the initial responsiveness testing period should be defined as a $\geq 30\%$ reduction in blood Phe levels from baseline. The PBAC considered that this is consistent with the guidelines and clinical data, and represents a reasonable balance between sensitivity and specificity.
- 6.7 For continuing access beyond this, the PBAC considered that regular routine follow-up was necessary to ensure that sapropterin is not used as a replacement to diet, and that a requirement around this should be included in the PBS restriction.
- 6.8 The PBAC considered that any continuation requirements based on Phe levels would potentially be confounded by intra-patient variability. Thus, the PBAC considered that the risk of use in patients not continuing to respond would be better managed through an RSA, rather than the PBS restriction.
- 6.9 The PBAC reiterated its previous consideration that the claims of superior comparative effectiveness and non-inferior comparative safety versus a Phe-restricted diet (relaxed or strict diet) were reasonable.
- 6.10 While the PBAC considered that the incremental cost-effectiveness ratio estimated in the resubmission was high, the Committee acknowledged the high clinical need in this small patient group and considered that the clinically significant outcomes in patients under the age of 18 may not have been fully captured in the economic evaluation. As such, the PBAC advised that inclusion of an RSA with ██████% rebate above the projected patient population was adequate to address its previous concerns around cost-effectiveness.

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- 6.11 The PBAC noted that the resubmission and pre-PBAC response had significantly lowered the estimated cost to the PBS over six years from more than \$100 million in the March 2018 submission to \$30 - \$60 million in the pre-PBAC response. In doing so, the resubmission and pre-PBAC response had addressed the PBAC's previous concerns around the financial estimates including that:
- the sapropterin doses for the initial period of responsiveness testing (up to one month) were included in the estimates, with [REDACTED] these doses to be rebated through an RSA. However, the PBAC noted these were based on a 28-day response testing period and may need to be adjusted for the shorter response testing periods outlined in the recommended restriction (24 hours for newborns and 7 days for older children and adolescents);
 - utilisation was updated to reflect the eligible population comprising patients aged 0 to 17 years as well as those who continue PBS-subsidised sapropterin once they turn 18 years of age; and
 - the eligible population, uptake rate and compliance rates were revised in the pre-PBAC response to reflect values that the PBAC considered were reasonable.
- 6.12 The PBAC noted that the resubmission estimated that [REDACTED]% of patients would respond to initial sapropterin responsiveness testing. The PBAC considered this estimate remained uncertain given the heterogeneity between the studies it was based on (in terms of sapropterin dose and the patient population), and a potential lack of applicability to the PBS population. However, the PBAC considered that the [REDACTED]% response rate was reasonable as it represented a mid-point between the response rates observed in a range of studies that used 24-hour and 7-day testing periods, and was based on data that was likely to be the best available.
- 6.13 The PBAC noted that the pre-PBAC response had proposed an RSA rebate such that the cost of sapropterin for continuing patients aged ≥ 18 years [REDACTED]. The PBAC noted this would reduce the financial impacts and may improve the cost-effectiveness in this group of continuing patients.
- 6.14 The PBAC noted that the pre-PBAC response had proposed an RSA with [REDACTED]% rebates on expenditure above the estimated net cost to the PBS (in addition to the [REDACTED]% rebate on the cost to the PBS of all sapropterin used for initial responsiveness testing, and a partial rebate for patients aged ≥ 18 years). The PBAC noted that based on the sponsor's proposal to provide responsiveness testing doses [REDACTED] and a rebate for patients aged ≥ 18 years, these should be deducted from the calculation of the RSA financial cap to ensure caps are set at the expected actual cost to Government. The PBAC considered an RSA at the level of the estimated utilisation and [REDACTED]% rebate above the financial caps was appropriate and was necessary to manage the high and uncertain cost-effectiveness, the uncertain patient population, including the risk of use in patients not continuing to respond.
- 6.15 The PBAC advised that sapropterin is suitable for prescribing by nurse practitioners.
- 6.16 The PBAC recommended that the Early Supply Rule should apply.

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6.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 **Add new listing:** Restriction to be finalised. Indicative restrictions are outlined below.

Initial responsiveness testing

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity	-
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Initial – responsiveness testing
Restriction method	Authority Required – in Writing
Treatment criteria	Must be treated by a metabolic physician, or by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Clinical criteria	<p>Patient must have blood phenylalanine level above 360 µmol/L if the patient is less than one month of age; OR</p> <p>Patient must have blood phenylalanine level above 600 µmol/L if the patient is aged one month to less than 18 years;</p> <p>AND</p> <p>The treatment must be for the purposes of responsiveness testing;</p> <p>AND</p> <p>Patient must have signed a patient or parent/guardian acknowledgement indicating that they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment.</p>
Population criteria	The patient must be under 18 years of age
Prescriber instructions	<p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) A completed authority prescription form (b) A completed Hyperphenylalaninemia (HPA) due to phenylketonuria PBS Authority Application – Supporting Information Form which includes the following: <ul style="list-style-type: none"> (i) Baseline blood phenylalanine levels prior to sapropterin responsiveness testing (ii) Responsiveness testing trial commencement date (iii) Documented diagnosis of PKU (iv) A signed patient acknowledgement <p>Dietary phenylalanine intake must be maintained at a constant level during the responsiveness testing period.</p> <p>Responsiveness testing period must be for 24 hours in patients aged less than one month and 7 days in patients aged one month to less than 18 years.</p>

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	<p>Patients or their parent/guardian should be assessed for their ability to comply with the sapropterin protocol and PKU diet prior to conducting initial responsiveness testing.</p>
Administrative advice	<p>Special pricing arrangements apply</p> <p>Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment with sapropterin to be assessed.</p> <p>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).</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

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First continuing restriction

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity	-
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	First continuing
Restriction method	Authority Required – in Writing
Treatment criteria	Must be treated by a metabolic physician, or by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Clinical criteria	Patient must have previously received initial PBS-subsidised treatment with this drug for this condition for the purposes of responsiveness testing; AND Patient must have demonstrated a response to treatment with this drug of greater than or equal to a 30% reduction in phenylalanine levels from baseline during initial responsiveness testing.
Population criteria	Patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition.
Prescriber instructions	The authority application must be made in writing and must include: <ul style="list-style-type: none"> (a) A completed authority prescription form (b) A completed Hyperphenylalaninemia (HPA) due to phenylketonuria PBS Authority Application – Supporting Information Form which includes: <ul style="list-style-type: none"> (i) blood phenylalanine levels during sapropterin responsiveness testing <p>Blood phenylalanine levels must be based on measurements taken during stable periods of the condition.</p> <p>Dietary phenylalanine intake must be maintained at a constant level.</p>
Administrative advice	Special pricing arrangements apply Patients will be eligible for a maximum of 1 script and 5 repeats as first continuing therapy. 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 Complex Drugs Reply Paid 9826 HOBART TAS 7001

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Subsequent continuing restriction

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity	-
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Subsequent continuing
Restriction method	Authority Required – in Writing
Treatment criteria	Must be treated by a metabolic physician, or by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Clinical criteria	Patient must have received First Continuing PBS-subsidised treatment with this drug for this condition; OR Patient must have received Grandfather PBS-subsidised treatment with this drug for this condition; AND Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications.
Population criteria	Patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition.
Prescriber instructions	The authority application must be made in writing
Administrative advice	Special pricing arrangements apply 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 Complex Drugs Reply Paid 9826 HOBART TAS 7001

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Grandfather restriction

Category/Program	Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity	-
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Grandfather treatment
Restriction method	Authority Required – in Writing
Treatment criteria	Must be treated by a metabolic physician, or by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Clinical criteria	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to {listing date}</p> <p>AND</p> <p>Patient must have demonstrated a response to treatment with this drug of greater than or equal to 30% reduction in phenylalanine levels from baseline during initial responsiveness testing.</p>
Population criteria	Patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition.
Prescriber instructions	<p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) A completed authority prescription form (b) A completed Hyperphenylalaninemia (HPA) due to phenylketonuria PBS Authority Application – Supporting Information Form which includes: <ul style="list-style-type: none"> (i) blood phenylalanine levels at baseline (ii) blood phenylalanine levels during sapropterin responsiveness testing (iii) documented diagnosis of PKU <p>Blood phenylalanine levels must be based on measurements taken during stable periods of the condition.</p> <p>Dietary phenylalanine intake must be maintained at constant levels.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a grandfathered patient must qualify under the Subsequent continuing treatment criteria.</p>
Administrative advice	<p>Special pricing arrangements apply</p> <p>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).</p> <p>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</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

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

BioMarin welcomes the positive recommendation and would like to thank the PBAC for its consideration of PKU. Further, BioMarin would also like to recognise the input received from patients, families and health care professionals.