

**6.09 SAPROPTERIN,
Tablet (soluble) containing sapropterin
dihydrochloride 100 mg
Powder for oral solution 500 mg (as dihydrochloride),
Kuvan[®],
BioMarin Pharmaceutical Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested an extension to the current PBS listing for sapropterin for the treatment of hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) to allow adults to be eligible for sapropterin responsiveness testing and continuing treatment for those who are sapropterin responsive.
- 1.2 Sapropterin is currently PBS-listed for initiation in patients who are < 18 years old, and, once initiated, patients can continue in adulthood. The requested extension would allow initiation of sapropterin in patients aged ≥ 18 years old. Additionally, the submission requested an amendment to the administrative notes to allow patients who failed a 24-hour test prior to 1 month of age to have the opportunity to retest one additional time at >1 month of age.
- 1.3 The sponsor also requested listing of pegvaliase for HPA due to PKU in patients aged ≥16 years who are unresponsive to sapropterin. The sponsor presented the two requests in the same document, while the evaluation, ESC Advice and PBAC considerations are presented as separate documents. The pegvaliase and sapropterin submissions share some key components of the economic and financial evidence (e.g. economic model structure).
- 1.4 Listing was requested on the basis of a cost-effectiveness analysis versus a phenylalanine (Phe)-restricted diet.
- 1.5 Key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Adults with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) and who are sapropterin responsive
Intervention	Sapropterin 5-20 mg/kg/day, oral administration
Comparator	Phenylalanine (Phe)-restricted diet
Outcomes	Reduction in blood Phe levels by > 30% from sapropterin-naïve baseline
Clinical claim	Sapropterin in combination with a Phe-restricted diet is superior to a Phe-restricted diet alone. Sapropterin has non-inferior safety compared with a Phe-restricted diet alone.

Source: Table 1.1-1, p5 of the submission.

2 Background

Registration status

2.1 Sapropterin was approved by the TGA in October 2010 for the following indication:

- The treatment of hyperphenylalaninemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency.

Previous PBAC consideration

2.2 The PBAC has considered submissions for sapropterin at the following meetings:

- November 2011: sapropterin for HPA due to PKU or HPA due to BH4 deficiency in patients aged a) 10 years or younger, b) 11 to 17 years and c) 18 years of age or older – not recommended
- July 2012 resubmission: HPA due to BH4 deficiency with no age restriction – deferred
- November 2012 minor resubmission: HPA due to BH4 deficiency with no age restriction – recommended under rule of rescue
- March 2018 major resubmission: HPA due to PKU with no age restriction - deferred
- November 2018 minor resubmission: HPA due to PKU in patients commencing treatment when aged < 18 years - recommended
- July 2019 minor resubmission: new dosages (100 mg and 500 mg powder for oral solution) in HPA due to PKU - recommended
- November 2020 minor resubmission: HPA due to maternal PKU (MPKU) in patients who are 18 years or older who have not previously initiated treatment with sapropterin - recommended

2.3 Key issues from the most recent considerations (excluding the Maternal PKU November 2020 Public Summary Document (PSD)) are presented in Table 2.

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Table 2: Summary of key matters of concern

Component	Matter of concern		How the resubmission addresses it
	March 2018	November 2018	
Population	The PBAC sought further evidence regarding processes for determining whether or not a patient is responsive to sapropterin in terms of clinically significant outcomes such as cognitive function and supporting growth. The PBAC considered that commencement of sapropterin therapy should be restricted to children and adolescents (paras 7.1 -7.4, March 2018 PSD)	PBAC reiterated previous consideration that sapropterin should only be commenced in patients who are younger than 18 years of age (para 6.2, November 2018 PSD)	No new comparative data were presented to provide further evidence of cognitive outcomes. Some published literature was briefly referred to in Section 1 and was used as a premise for modelling benefit in the economic evaluation.
Economic Analysis	The PBAC considered that the ICER was unreliable as it was based on: <ul style="list-style-type: none"> • utility weights that lacked face validity. • weighting the ICER between two sub-groups • epidemiological data that were not applicable to the Australian population. The PBAC considered that the resulting ICER for patients aged 18 years and over, of more than \$200,000/QALY, was unacceptably high. (paras 7.12-13, March 2018 PSD)	While the PBAC considered that the ICER estimated in the resubmission was high, the PBAC considered that the clinically significant outcomes in patients under the age of 18 may not have been fully captured in the economic evaluation.	A new microsimulation model was presented. The ICER remained high.
Financials/ RSA	Revised RSA was required based on updated financial estimates. (para 7.17, March 2018 PSD)		Updated Financials and RSA

Source: Sapropterin March 2018 PSD and Sapropterin November 2018 PSD

2.4 The maternal PKU November 2020 PSD also included PBAC considerations relevant to the current submission. These are presented in Table 3.

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Table 3: Relevant matters of concern in the MPKU November 2020 submission

Component	Relevant Matter of concern	Comment
	November 2020	
Population	The PBAC acknowledged there is a high clinical need for sapropterin in non-MPKU patients. The PBAC acknowledged the consumer comments that supported a broader listing for any adult with PKU given the likely improvements in cognitive function, mental health and social inclusion. While the impact of PKU on neurological function is more subtle and reversible in adults than it is in babies and children, the PBAC considered that sapropterin is associated with important quality of life benefits in a broader adult population. (paragraph 7.3)	Overall, the PBAC considerations pointed to an acknowledgment of superiority of sapropterin in the overall adult PKU population, but that the magnitude of such benefit is challenging to ascertain. In the MPKU population, the submission noted that cost-effectiveness may be considered on the basis of future impacts on the unborn child.
Clinical	The PBAC considered that the clinical data presented in this submission and the previous submissions demonstrated that, in all adults, sapropterin has superior comparative effectiveness and non-inferior comparative safety versus a Phe-restricted diet alone. (paragraph 7.8) The PBAC considered the clinical benefits of reductions in maternal Phe levels are potentially greater than for the overall PKU population, and more closely resemble the benefits achieved for patients aged under 18 years. (paragraph 7.9)	
Economic Analysis	The PBAC considered that while the estimated ICER is high, the economic analysis presented was based on the outcome of the mother's quality of life while she is on treatment, and did not consider the impact on the unborn child. (paragraph 7.10) A resubmission should address issues raised previously by the PBAC, including that the economic model was not reliable for the broader adult population. (paragraph 7.14)	

Source: Sapropterin November 2020 PSD

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Initial treatment- responsiveness testing			\$817.00 (published price)	
Sapropterin dihydrochloride 100 mg soluble tablet, 30	30	0	\$█ (effective price)	
Sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	30	0	\$4,085.00 (published price) \$█ (effective price)	KUVAN BioMarin
First & subsequent Continuing treatment			\$817.00 (published price)	
Sapropterin dihydrochloride 100 mg soluble tablet, 30	30	5	\$█ (effective price)	
Sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	30	5	\$4,085.00 (published price) \$█ (effective price)	
Category/Program:	General Schedule			
PBS indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)			
Treatment phase:	Initial treatment - responsiveness testing			
Clinical criteria:	Patient must not have previously received PBS-subsidised treatment with this drug for this condition; AND Patient must have a baseline blood phenylalanine level above 360 micromole per L and be less than one month of age; OR			

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	Patient must have a baseline blood phenylalanine level above 600 micromole per L and be more than one month of age; AND The treatment must be for the purpose of initial responsiveness testing for a period of 24 hours in a patient less than one month of age; OR The treatment must be for the purpose of initial responsiveness testing for a period of 7 days in a patient aged more than one month
Population criteria:	Patient must be under 18 years of age.
Treatment criteria:	Must be treated by a metabolic physician
Prescriber instructions:	Dietary phenylalanine intake must be maintained at a constant level. 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
Administrative advice	Special pricing arrangements apply. Patients will be eligible for a maximum of one PBS subsidised prescription at less than one month of age and one PBS subsidised prescription at more than one month of age as initial therapy to enable their response to treatment with sapropterin to be assessed.
Treatment phase:	First continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment under the Initial - responsiveness testing restriction with this drug for this condition; 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.;
Treatment criteria:	Must be treated by a metabolic physician; or Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Prescriber instructions:	Blood phenylalanine levels must be based on measurements taken during stable periods of the condition. Dietary phenylalanine intake must be maintained at a constant level.
Administrative advice	Special pricing arrangements apply
Treatment phase:	Subsequent continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction; AND Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications
Treatment criteria:	Must be treated by a metabolic physician; or Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
Administrative advice	Special pricing arrangements apply

Criteria in bold indicates requested changes to current PBS listing

Source: Tables 1.4-5 to 1.4-7, pp42 - 44 of the submission.

- 3.1 The requested effective price is the same as for the existing sapropterin listing.
- 3.2 The key change proposed to the existing sapropterin listing was removal of the population criterion: 'patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition'. Thus, patients aged 18 years

and older with a blood Phe >600 µmol/L would undergo the same 7-day sapropterin responsiveness test that is currently conducted for patients aged 1 month to less than 18 years of age. A response to sapropterin is defined as a reduction in blood Phe by >30% compared with sapropterin-naïve baseline. The published clinical guidelines presented in the submission consider that the Phe level for initiating treatment (dietary or pharmacological) was >360 µmol/L in patients >12 years old, and consequently the requested population may be narrower than that recommended in guidelines. The 600 µmol/L threshold was consistent with the inclusion criteria for the PKU-001 trial and the existing listing.

- 3.3 The submission also requested an amendment to the administrative notes enabling patients who failed a 24-hour test prior to 1 month of age to have the opportunity to retest one additional time at >1 month of age. This change would allow patients who failed to respond to sapropterin when they were <1 month of age to trial sapropterin again. The submission did not further discuss this change and presented no specific evidence to support the change. Patients who had an additional test after 1 month of age would not meet the first clinical criterion of: “Patient must not have previously received PBS-subsidised treatment with this drug for this condition”.
- 3.4 With the requested changes to the restriction the only additional patients who would access sapropterin would be:
- 1) adult patients who had never accessed sapropterin (predominantly those who were at least 18 years at the time of PBS-listing of sapropterin); and
 - 2) Patients under 18 years of age who failed a 24-hour test prior to 1 month of age and retest one additional time at greater than 1 month of age.
- 3.5 The submission proposed the same definition of response as applies in the existing sapropterin restrictions, which is based on a reduction in blood Phe of >30% compared with sapropterin-naïve baseline assessed over a 7-day period. The PBAC noted that consumers and clinicians had outlined that factors other than Phe levels may also be important markers of a meaningful improvement for patients, such as protein tolerance/dietary Phe intake, quality of life and an assessment as to how well a patient is managing with their current regimen. Consumers and clinicians had also outlined that a 7-day response assessment period may be too short to assess some of these factors, and that the current testing arrangement relies on patients maintaining a constant diet for seven days which is difficult to achieve. The PBAC considered that a change to the definition of response for the sapropterin restrictions may be appropriate and noted that expert clinical consultation would be required in order to determine the most appropriate (if any) change to the response criterion.

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

4 Population and disease

- 4.1 PKU is a rare inborn disorder which leads to HPA whereby patients suffer from elevated levels of the essential amino acid phenylalanine (Phe) in the blood. In patients with PKU, the enzyme phenylalanine hydroxylase (PAH) does not effectively metabolise Phe into the essential amino acid tyrosine due to mutations in the PAH gene causing PAH deficiency.
- 4.2 In adults, untreated high Phe-blood levels can cause neuropsychiatric symptoms including inattention, hyperactivity, anxiety, depression, seizures and tremors. This can impact executive function, which is a collection of cognitive skills that are required to self-regulate and organise mental efforts in order to achieve goals (Bilder et al., 2016). The ability to plan and organise are critical skills required in adulthood, and poor executive function as a result of elevated blood Phe can have negative impacts on a person's employment and relationships, as well as their ability to appropriately manage their PKU.
- 4.3 The PBAC had previously considered that the benefits of sapropterin therapy in terms of improved neurological function were likely to be greatest during the development period for children and adolescents as untreated elevated blood-Phe levels during developmental stages can lead to mental retardation, neurocognitive deficits, behavioural abnormalities, seizures and other serious neurological complications (paragraphs 4.2, 7.1 and 7.3, sapropterin PSD, March 2018 PBAC meeting).
- 4.4 Patients often maintain their Phe-levels via a Phe-controlled diet, consisting of low-protein foods combined with PBS-subsidised Phe-free supplements. PKU patients experience negative quality-of-life (QoL) impacts through neuropsychiatric symptoms and executive functioning impacts, but also through the negative impacts of a Phe-restrictive diet.
- 4.5 Sapropterin dihydrochloride is a synthetic version of the naturally occurring tetrahydrobiopterin (BH4), which is a cofactor for PAH. Sapropterin acts by enhancing the activity of the defective PAH allowing Phe to be more effectively metabolised. It appears to work best for certain mutations of the defective enzyme. Hence there is a subgroup of patients with PKU who are 'responsive' to sapropterin. The defective enzymes that are significantly enhanced by sapropterin are generally those that have considerable residual activity. Thus, patients who are most likely to respond to sapropterin are those with lower baseline Phe levels and 'milder' disease. In patients with sapropterin-responsive PKU, sapropterin increases or restores the oxidative metabolism of Phe by PAH to reduce blood Phe levels and/or improve Phe tolerance (i.e. increasing dietary intake of Phe while maintaining blood Phe levels within the target range). On the other hand, pegvaliase is an enzyme substitution therapy, which unlike sapropterin, is not reliant on the patient having any residual endogenous PAH activity.

- 4.6 Sapropterin is intended to be used in conjunction with a Phe-restricted diet. In clinical practice, it is likely that at least some of the benefit to patients of sapropterin treatment will be due to a relaxation of dietary Phe-restrictions.
- 4.7 Response to sapropterin can only be determined by a therapeutic trial of sapropterin. The PI stated that the starting dose of sapropterin in adult and paediatric patients with PKU is 10 mg/kg body weight once daily. The dose is adjusted to achieve and maintain adequate blood phenylalanine levels as defined by the physician. The recommended daily dose is between 5 and 20 mg/kg/day.

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

5 Comparator

- 5.1 The submission nominated a Phe-restricted diet alone as the comparator. This was also the nominated comparator in the most recent November 2020 resubmission for sapropterin in patients aged ≥ 18 years with MPKU, and was considered by the PBAC as appropriate and consistent with previous submissions for PKU (paragraph 5.1, sapropterin November 2020 PSD).
- 5.2 The submission considered that the Phe-restricted diet was the mainstay of therapy for HPA due to PKU and that all patients should be on a Phe-restricted diet.
- 5.3 The submission noted that, for consistency with previous PBAC submissions for sapropterin for the treatment of PKU, the submission considered that a Phe-restricted diet comprises the following:
- Natural protein restriction according to individual Phe tolerance;
 - PBS-listed Phe-free amino acid supplements (with added vitamins and minerals) to meet protein and non-protein requirements; and
 - Low-protein food to meet energy requirements.
- 5.4 The submission considered that sapropterin would not be expected to replace a Phe-restricted diet but would rather be used in combination with it. However, the submission also considered that adherence to the Phe-restricted diet tended to be low, consequently it was unclear whether sapropterin would in practice, serve as a replacement. DUSC has previously considered that sapropterin use may allow inappropriate relaxation of the Phe-restricted diet (paragraph 6.70, sapropterin, PSD, March 2018 PBAC meeting).
- 5.5 In the concurrent pegvaliase submission, pegvaliase was specifically requested for patients who had not responded to sapropterin and hence the submission considered it would not be a comparator. However, the evaluation and ESC considered that the restriction of pegvaliase to sapropterin non-responders was poorly justified and in practice it may be difficult to distinguish two separate lines of therapy. Consequently,

should the clinical use of pegvaliase be broader than requested by the sponsor, pegvaliase may be a near-market comparator to sapropterin.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The PBAC noted that the sponsor requested a hearing for pegvaliase which was also relevant for sapropterin. The two clinicians described the real world, functional impact of high Phe levels on patients including high rates of depression, anxiety and panic attacks and also the impacts on cognitive function in terms of reduced working memory, attention and mood. The clinicians stated that even small reductions in Phe levels can improve these outcomes and consequently improve patients' ability to manage their diet, daily life, family and work. One clinician noted that these outcomes are clinically evident but are difficult to study and were not well-captured in the trials.

Consumer comments

- 6.2 Representatives of the PBAC met with patient and health professional representatives prior to the PBAC meeting. The following is a summary of the perspectives presented:
- Diet management alone is extremely difficult and has an enormous impact on patients. Many patients struggle to lower or maintain their Phe levels using diet alone.
 - Dopamine depletion results in reduced executive function and serotonin depletion results in anxiety and depression, though cognitive function and psychiatric well-being impacts are experienced at variable levels.
 - Reductions in Phe levels in adults can lead to significant and meaningful improvements, with depression and anxiety scores improved and working memory and cognitive function substantially improved or returned over the longer term¹. Clinicians also highlighted that there is evidence that patients experience reversible changes in white matter indicative of neurodegenerative effects of raised blood Phe levels².
 - The sponsor's proposed management algorithm, which positioned pegvaliase as a second-line treatment for those patients who are not responsive to sapropterin, was not considered to be appropriate (also outlined in Paragraph 6.3).

¹ Burgess NM, Kelso W, Malpas CB, Winton-Brown T, Fazio T, Panetta J, De Jong G, Neath J, Atherton S, Velakoulis D, Walterfang M. The effect of improved dietary control on cognitive and psychiatric functioning in adults with phenylketonuria: the ReDAPT study. *Orphanet J Rare Dis.* 2021 Jan 18;16(1):35. doi: 10.1186/s13023-020-01668-2. PMID: 33461585; PMCID: PMC7814424.

² Anderson PJ, Leuzzi V. White matter pathology in phenylketonuria. *Mol Genet Metab.* 2010;99 Suppl 1:S3-9. doi: 10.1016/j.ymgme.2009.10.005. PMID: 20123467.

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- Treatment with sapropterin has been life-changing for some patients, while others have only experienced a minimal response in terms of meaningful changes to diet or effects on cognitive function, so there is a high clinical need for alternative treatment options.
 - Blood Phe levels should not be the single measure of assessment for determining response to treatment or optimal therapy for overall patient benefit. Meaningful improvement could also be defined in terms of protein tolerance/dietary Phe intake, QoL and how well a patient manages on their current regimen.
- 6.3 The PBAC noted and welcomed the input from health professionals (3), individuals (102) and organisations (2).
- 6.4 The Metabolic Dietary Disorders Association and PKU Association of NSW (MDDA & PKUNSW) noted the importance of equitable access to treatments for all Australians with PKU. The MDDA & PKUNSW noted that sapropterin and pegvaliase work differently and have different advantages and disadvantages. Decisions about which treatment a patient uses should be made by a clinician in consultation with the individual considering clinical need and personal circumstances.
- 6.5 The MDDA & PKUNSW also described the burden of the restrictive diet and complexity of managing PKU, the limitations and unsustainability of dietary management and the impact of PKU on every aspect of life.
- 6.6 Rare Voices Australia (RVA) discussed the advantages of sapropterin including its impact on: reducing blood Phe concentration; increasing natural protein tolerance; improving health outcomes; decreasing co-morbidities; improving quality of life; and, importantly, improving neurocognitive functioning and mental wellbeing. RVA supported extending the current PBS listing for sapropterin to allow initiation in adults, stating that this extension would remove an inequitable barrier to access.
- 6.7 All comments from health professionals, individuals with PKU and other interested individuals were supportive of allowing access to sapropterin regardless of age.
- 6.8 Comments from individuals with PKU and their carers discussed the difficulties of accessing and adhering to a low protein diet including the difficulties and time involved in preparing and following a low protein diet, the effects on family, school, and social life, and the exclusion that this creates for those affected. Patients are limited to eating high carbohydrate foods, cannot access a varied diet, and often do not feel satiated resulting in weight gain. Many patients need to supplement their diet with amino acid formula multiple times per day, which was described as unpalatable and difficult to adhere to.
- 6.9 Individuals who would like access to sapropterin to treat their PKU, and the carers and supporters of those with PKU, discussed the difficulties of maintaining low Phe levels with dietary management alone. Even when the diet is strictly adhered to, this may be insufficient to maintain an acceptable Phe level. Monitoring the levels and making the necessary dietary adjustments in a timely fashion was also an issue for many. The

comments also described issues with accessing food supplements and low protein foods in terms of cost and unreliable supply chains.

- 6.10 The inequity of the current age-based restriction was consistently noted by consumers, including concern that the current restrictions are not reasonable for many women who may be eligible for sapropterin access during conception and pregnancy, then need to cease therapy after childbirth, even though they have proven to be responsive to therapy.
- 6.11 Some individuals with PKU reported that compliance to protein-restricted diets becomes more difficult as patients enter adulthood once they take responsibility for their own diet, as adherence is made more difficult due to the challenges of PKU (fatigue, brain fog, mood disturbance).
- 6.12 The quality of life benefits of sapropterin therapy were strongly reinforced by patients who have been treated with sapropterin, and also their families and carers. This included improvements in psychosocial and cognitive function, energy levels, and managing self-care and tasks on a daily basis. The comments outlined that increased protein tolerance was an important outcome, as it enabled patients to eat a broader range of foods, alleviating the burden of living with a severely low protein diet.

Clinical studies and trials

- 6.13 The submission was based on five studies that reported changes in blood Phe levels with sapropterin treatment:
- PKU-001 (N=490), an open label single arm study to evaluate the safety and efficacy of an eight-day course of sapropterin.
 - PKU-003 (N= 88): a double blind randomised, placebo-controlled trial comparing six weeks of treatment with sapropterin (in addition to a Phe-restricted diet) with placebo (dietary control of Phe alone), in known responders to sapropterin and tolerance to normal diet. This is the only direct comparative evidence for sapropterin compared to placebo available.
 - Two extension studies (PKU-004: N=80; and PKU-008: N = 111) examining dose response and safety were included as supporting studies. Patients in PKU-004 received sapropterin for 22 weeks, and the median duration of treatment in PKU-008 was 595 days.
 - The Phenylketonuria (PKU) Demographics, Outcomes and Safety (PKUDOS; N=1189) registry of patients with PKU who were, or had been, treated with sapropterin. Of the enrolled patients, 504 were continuously exposed to sapropterin from the date of registry enrolment, 211 had intermittent exposure to sapropterin, and 474 had some other duration of exposure. The submission claimed the median duration of follow up was not reported. The PBAC has previously reviewed data from the PKUDOS registry that had a cut-off date of June 2013 (as reported in Longo 2015). The submission presented two more recent

data-cuts: data cut-off February 2017 from a conference poster (Lilienstein 2018); and a post-hoc analysis from May 2016 (subgroup of patients aged 18 years or older at first use of sapropterin who had a baseline Phe > 600 µmol/L).

- 6.14 In contrast to the previous submissions, the KAMPER European Observational program and the ENDURANCE sapropterin responsiveness study were excluded from the current submission. The submission considered that the baseline blood Phe levels in ENDURE (465.1 ± 228.2 µmol/L) and in KAMPER (median: 544.9 µmol/L; mean: 615 µmol/L pre-sapropterin, in patients aged ≥ 18 years) were not consistent with the clinical criteria of the requested restriction which specified > 600 µmol/L. However, these studies were included in the previous submissions which also had the same > 600 µmol/L criteria. As patients in KAMPER were already on sapropterin it would be expected that their Phe levels would be < 600 µmol/L and inclusion criteria for ENDURE required patients to have Phe levels > 400 µmol/L. Overall, the evaluation and the ESC considered it was unclear if it was reasonable to exclude these studies. The limited information provided about KAMPER in the submission appeared to show that dietary intake of natural protein increased from 30.0 g/day prior to sapropterin treatment, to 50.1 g/day after one year of sapropterin (n = 28 at both time points), while blood Phe levels decreased from a mean of 615 µmol/L pre-sapropterin (n = 67) to 491 µmol/L (n = 59).
- 6.15 With the exception of the more recent data cuts of the PKUDOS registry data, all of the aforementioned studies had previously been reviewed by the PBAC. The Pre-Sub Committee Response (PSCR) and pre-PBAC response reiterated that the totality of the evidence has been presented.
- 6.16 The submission also presented a review of translational studies discussing the relationship between blood-Phe and improvements in neuropsychiatric symptoms; and Phe tolerance (increase in dietary Phe intake) with quality of life in adult PKU patients.
- 6.17 Details of the trials and studies presented in the submission are provided in Table 4.

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Table 4: Trials and associated reports presented in the submission

Trial ID`	Protocol title/ Publication title	Publication citation
PKU-001	A Phase 2, Multicenter, Open-Label Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin™ (sapropterin dihydrochloride) Treatment in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels	December 2006
	An Open-label Substudy to Evaluate Phenylalanine Levels Over a Twenty-Four Hour Period in Subjects with Phenylketonuria Participating in the PKU-001 Study	December 2006
	A Phase 2, Multicenter, Open-Label Study to Evaluate the Response to and Safety of an 8-Day Course of Kuvan® (sapropterin dihydrochloride) Treatment in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels	December 2008
	Burton et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study.	Journal of Inherited Metabolic Disease 2007; 30:700–707
PKU-003	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin™ (sapropterin dihydrochloride) in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels	December 2006
	Levy et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study.	Lancet 2007; 370: 504-510
PKU-004	A Phase 3, Multicenter, Open-Label Extension Study of Phenoptin™ (sapropterin dihydrochloride) in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels	March 2007
	Lee et al. Safety and Efficacy of 22 Weeks of Treatment With Sapropterin Dihydrochloride in Patients With Phenylketonuria.	American Journal of Medical Genetics 2008; Part A 146A:2851–2859
PKU-008	A Phase 3b, Multicenter, Open-Label Extension Study of Phenoptin™ (sapropterin dihydrochloride) in Subjects with Phenylketonuria Who Participated in Studies PKU-004 or PKU-006;	April 2010
	Burton et al. Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: Results of a phase 3b study.	Molecular Genetics and Metabolism 2011; 103: 315–322
Supplemental studies		
PKUDOS	Longo et al., Long-term safety and efficacy of sapropterin: The PKUDOS registry experience.	Mol Gen Metab 2015; 557-563
	Lilienstein et al. Interim analysis of the Phenylketonuria (PKU) patients enrolled in the PKUDOS registry.	Presented at the National PKU Alliance Conference, July 5-8 2018, Atlanta, GA, US [poster]

Source: Table 2.8.10, p175 of the submission.

6.18 Key features of included key evidence is presented in Table 5.

Table 5: Key features of the key evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
PKU-001	490	OL, SAS 8 day duration	NA	Patients ≥ 8 years, not adhering to a strict Phe-restricted diet blood Phe levels were defined as ≥ 600 µmol/L (original protocol) or 450 µmol/L (after Protocol Amendment)	Response to 8 days of sapropterin 10 mg/kg/day Response defined as a ≥ 30% reduction in blood Phe level from Day 1 (pre-sapropterin) to Day 8	No
PKU-003	88	R, DB, 6 week duration	Low	PKU-001 patients demonstrating a response to sapropterin 10 mg/kg	•Reduction in blood Phe-levels from baseline to week 6 •Mean change in blood Phe over 6 weeks •Proportion of patients with blood Phe < 600 µmol/L	No
PKUDOS	1189	Registry	NA	Documented blood Phe of ≥ 360 µmol/L and previous, current sapropterin use or intention to receive sapropterin within 90 days of enrolment	Mean relative change of Phe in responders; Mean absolute Phe Change in non-responders. Proportion of patients achieving 30% reduction in Phe after 7-28 days	Yes ^a .

Source: Table 2.8-11, p179 of the submission

DB = double blind; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised.

^aPost-hoc analyses of a separate unpublished May 2016 data cut in a small subset of patients

Blue shading indicate evidence previously considered by PBAC; Note that the PBAC has previously seen data from the PKUDOS registry through the resubmission presented two new data-cuts.

- 6.19 A key issue with the PKUDOS data and its subsequent incorporation into the economic model was that the analyses used data from adult patients who were continuously treated with sapropterin versus those who had discontinued sapropterin as a proxy for comparing patients who initiate sapropterin in adulthood (i.e. who had not received sapropterin in childhood) versus a Phe restricted diet alone. The PBAC noted that there were applicability issues with the use of these data as the populations were not directly representative of the PBS population for sapropterin or the relevant comparator and there were no studies presented in sapropterin-naïve adult patients.
- 6.20 PKU-003 was the only comparative study presented, with a duration of only six weeks. Comparatively, usage of sapropterin was proposed to be lifelong. Further, no subgroup data from adult patients enrolled in PKU-003 were presented (although it is acknowledged that subgroup analyses would be difficult to interpret due to small sample sizes). Full distributions of patients by age at baseline were not presented in the submission or CSR, but given that the median age was 18, at least half of the trial population reflected the extension population.
- 6.21 Though the submission considered that the provided evidence included a majority of adult patients (only sapropterin studies with at least half of the patients ≥ 18 years of age were included), none of the studies reported efficacy specifically in patients who initiated sapropterin as adults. This was a key applicability issue as the prevention of intellectual disabilities with early childhood control of blood Phe levels is a key benefit of controlling Phe levels, and the PBAC 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 (paragraph 7.1 and 7.3

sapropterin PSD, March 2018 PBAC meeting). As such, the magnitude of the incremental benefit in terms of lowering blood-Phe levels in adults was uncertain. International guidelines note that evidence is lacking in adult management goals (van Wegberg 2017).

Comparative effectiveness

6.22 Table 6 provides the results based on number of responders in PKU-001 and the comparative effectiveness results from PKU-003.

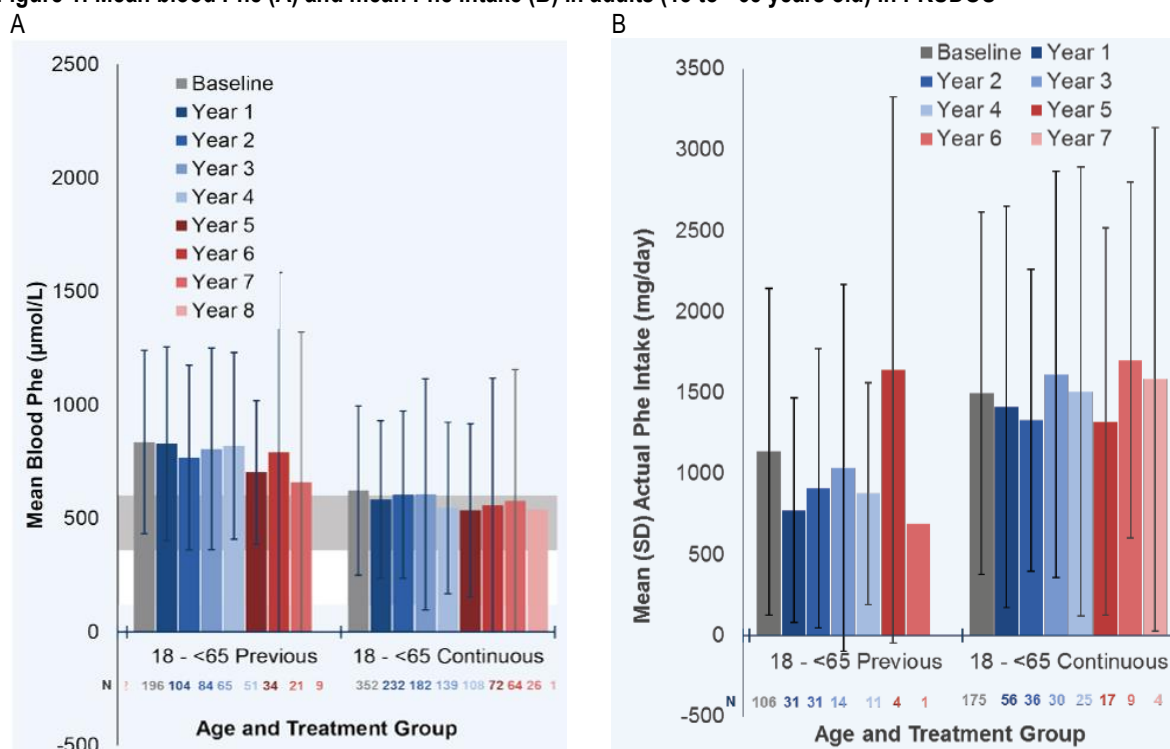
Table 6: Summary of effectiveness results previously considered by PBAC

Response to sapropterin, defined as $\geq 30\%$ reduction in blood Phe levels in studies PKU-001			
Study	Response		Patients
	n/N (%)	95% CI	
PKU-001, 10 mg/kg/day for 8 days	96/485 (20)	16, 23	≥ 8 years, baseline Phe ≥ 480 $\mu\text{mol/L}$, no strict diet
Responders by baseline blood-Phe			
<600 $\mu\text{mol/L}$	31/57 (54)	41, 68	
600-899 $\mu\text{mol/L}$	38/157 (24)	NR	
900-1119 $\mu\text{mol/L}$	14/135 (10)	NR	
≥ 1200 $\mu\text{mol/L}$	13/136 (10)	NR	
Results for the change in blood Phe levels reported in the PKU-003			
Trial/Study	Sapropterin	Placebo	Estimate (95% CI) between groups
PKU-003			
Baseline, mean $\mu\text{mol/L}$ (SD)	N=41, 842.7 (299.6)	N=47, 888.3 (323.1)	Difference = -245 (-350, -141)
6 weeks, mean $\mu\text{mol/L}$ (SD)	N=41, 606.9 (377.0)	N=47, 981.2 (347.6)	
Change, mean $\mu\text{mol/L}$ (SE)	N=41, -239 (38.3)	N=47, 6 (35.8)	
Proportion <600 $\mu\text{mol/L}$, n/N (%)	22/41 (54)	11/47 (23)	RR=2.3 (1.3, 4.1) RD=0.3 (0.1, 0.5)
Proportion <360 $\mu\text{mol/L}$, n/N (%)	13/41 (32)	1/47 (2)	RR=14.9 (2.0, 109.1) RD=0.3 (0.2, 0.4)

Source: Tables 7 and 8, pp14-15 of Sapropterin March 2018 PBAC PSD.
Blue shading indicate evidence previously considered by PBAC

- 6.23 In PKU-004, a reduction in blood Phe was observed at all time points (up to week 22) with treatment with sapropterin, with larger reductions observed with increasing doses of sapropterin, which were statistically significant ($P < 0.01$).
- 6.24 In PKU-008, the mean blood Phe remained constant in both cohorts over 24 months for both patients who continued treatment with sapropterin and who were previously enrolled in PKU-004 and PKU-006, though no statistical tests were conducted.
- 6.25 The submission also presented a more recent cut-off (February 2017) of the PKUDOS registry from Lilienstein (2018). The change in blood Phe levels over a follow-up of 8 years for adults (18 to <65 years) is presented in Figure 1.

Figure 1: Mean blood Phe (A) and mean Phe intake (B) in adults (18 to <65 years old) in PKUDOS



Source: Figure 2.8-9, p224 of the submission Adapted from Lilienstein et al (2018) Poster figure 1 and 3. Phe = phenylalanine; SD = standard deviation

Light shaded area represents blood Phe range 120-360 µmol/L.

Dark shaded area represents blood Phe range 360-600 µmol/L.

6.26 The submission stated that patients in PKUDOS on continuous treatment with sapropterin were able to maintain blood Phe levels in the range of 360-600 µmol/L through the 8 years of follow-up, while the mean blood Phe levels were all above 600 µmol/L in the previously treated cohort (i.e. patients who discontinued sapropterin for any reason). The mean baseline Phe level was lower in patients on continuous treatment compared with those previously treated based on visual inspection of available data (Lilienstein 2018 did not present mean baseline Phe in either group, a graphical presentation of Phe at baseline and follow-up is presented in Figure 1). The submission acknowledged that this may be because sapropterin is more effective in patients with less severe PKU. The evaluation and ESC considered that any incremental differences in Phe levels should be interpreted with caution as patients who discontinued sapropterin had higher mean baseline Phe levels in this analysis, suggesting that they had more severe disease. As such, any incremental benefit from sapropterin treatment based on any PKUDOS data was likely overestimated.

6.27 The submission also noted that during the 8 years of follow-up, Phe intake was lower in the previously treated cohort than the continuously treated cohort, despite higher blood-Phe levels (Figure 1). In the continuously treated cohort, Phe intake appears relatively stable. In the previously treated cohort, there was greater variation. This might be a reflection of the difficulty in maintaining a strict Phe-restricted diet. It was

noted that continuously treated patients also had a higher mean Phe intake, suggesting that patients treated with sapropterin may adopt a less stringent Phe-controlled diet. DUSC has previously considered that sapropterin use may allow inappropriate relaxation of the Phe-restricted diet (para 6.70, sapropterin, PSD, March 2018 PBAC meeting). It was also noted that relaxation of the Phe-restricted diet contributes partly to the improvement in quality of life in patients experiencing a decrease in blood-Phe with active treatment. The PBAC considered that while being able to relax the Phe restricted diet clearly has important quality of life benefits, the incremental benefit in terms of diet relaxation (between patients treated with sapropterin plus Phe-restricted diet compared to Phe-restricted diet alone) was not quantified in the submission.

Response rates

- 6.28 The submission derived response rates from a May 2016 post-hoc analysis of a subgroup of patients aged 18 years or older at first use of sapropterin, who had a baseline Phe > 600 µmol/L. This baseline Phe level was taken: pre-sapropterin in the ‘continuously treated’ sapropterin group; or post-sapropterin in the ‘previously treated’ Phe diet alone group.
- 6.29 The pre-PBAC response argued that baseline Phe levels were similar in this analysis (unlike the analysis by Lilienstein et al, 2018 shown in Figure 1) as “the mean baseline blood Phe of all patients treated with sapropterin [including non-responders] was 1,057 µmol/L compared with 1,113 µmol/L for Phe-restricted diet alone”, and that the small difference was unlikely to have biased the comparison.
- 6.30 Based on this post-hoc analysis of PKUDOS data, 27/115 (23.5%) of adult patients with baseline Phe >600 µmol/L who received sapropterin achieved a ≥ 30% reduction in blood Phe levels in the first 28 days after starting sapropterin. In the economic model it was assumed that 23.5% of patients achieved a response within 7 days (as per the response period in the PBS restrictions). As such the evaluation and ESC considered the response rate to sapropterin may be overestimated.
- 6.31 The submission and PSCR argued that that as response to sapropterin is typically rapid, it was reasonable to assume that similar results are obtained in the 28-day testing period (which is recommended in the sapropterin Product Information) as in the 7-day testing period. The 23.5% response rate was derived using data that included patients who had no Phe measurements in the 28 day period. There were 79 patients with at least one measurement within the first 28 days (n = 79), 34% of whom (27/79) had a ≥ 30% reduction in blood Phe from baseline. The PBAC previously concluded that given the high intra-patient variability in Phe levels, the PBS restriction should require a 24-hour testing period in newborns and a 7-day testing period in children and adolescents (para 7.7, sapropterin, PSD, March 2018 PBAC meeting; para 2.10, sapropterin, PSD, November 2018 PBAC meeting). The evaluation considered it was unreasonable to apply a 28-day response rate in the economic model when the PBS restriction specifies a 7-day testing period.

- 6.32 Based on an analysis restricted to patients who were known to have responded in the first 28 days of treatment (at least one Phe measurement less than 70% of the baseline value i.e. $\geq 30\%$ reduction), the mean percentage change in blood-Phe in those treated with sapropterin was estimated to be 61% (95% CI: 51%, 72%) of the baseline Phe level. This mean and standard deviation were used to inform the magnitude of blood Phe improvement in the microsimulation model.
- 6.33 The submission considered that, overall, despite day-to-day fluctuations, sapropterin treatment resulted in a rapid decline in blood Phe levels, which remained consistent over time in sapropterin responders and this assumption was applied to the economic model. Individual patient data from Appendix 5 to the submission showed that there was a great deal of variation in blood Phe levels over time for patients treated with sapropterin.

Neurological symptoms

- 6.34 Neuropsychiatric assessments in the PKUDOS registry were reported by investigators for a follow-up of 5 years. These are presented in Figure 2.

Figure 2: Psychiatric assessments at baseline and follow-up in PKUDOS, all patients with data (0 to <65 years)

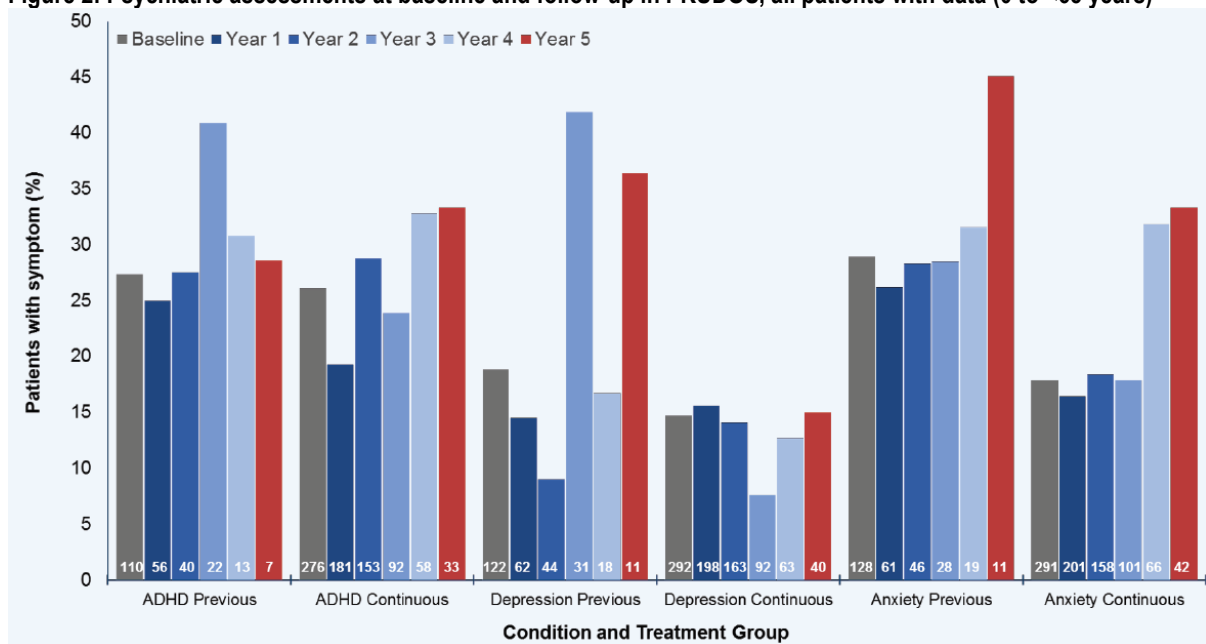


Figure 2.8.10, p225 of the submission.

ADHD = attention deficit hyperactivity disorder; OCD = obsessive compulsive disorder

Numbers inside bars correspond to the number of patients that were reported with these symptoms by investigators. Similar trends are seen in other psychiatric conditions assessed (OCD, phobia, autism, psychosis, and bipolar disorder).

- 6.35 The submission noted that these results were reported for patients with available data at baseline and follow-up time points and were not reported by age group and as such has limited applicability to the current submission. Among these patients, new cases of anxiety, ADHD, autism, depression and OCD generally decreased over time, the majority of which were mild or moderate.

- 6.36 Though these outcomes are clinically meaningful, the data do not allow any assessment of benefit in terms of these outcomes for adults.
- 6.37 Based on a literature review, the submission claimed that a lower blood Phe level was correlated with fewer neuropsychiatric symptoms in adults.
- 6.38 As part of the translational evidence, the submission presented results from PKU-016, a randomised controlled trial of sapropterin (n = 108) compared with placebo (n=98) as an adjunct to normal Phe-restricted diet in patients aged ≥ 8 years for 13 weeks. However, the submission excluded this trial as it did not include at least 50% adult patients. This trial reported no statistically significant differences between adults with PKU treated with sapropterin or placebo in ADHD-RS and BRIEF scores. The other translational evidence included published regression models from Bilder 2016 and Burgess 2021, which did not report any statistically significant correlations between Phe and neuropsychiatric outcomes.
- 6.39 Overall, while it was biologically plausible that a lower blood-Phe was correlated with fewer neuropsychiatric symptoms in adults, the evaluation and the ESC considered that the exact correlation was uncertain, and the incremental benefit associated with treatment with sapropterin was difficult to accurately quantify.
- 6.40 The submission also claimed that a relationship between increases in Phe tolerance and increased quality of life was supported by the time burden studies and HRQoL evidence. This was plausible and reasonable, and was captured in the time trade off (TTO) study used in the economic evaluation. However, differences in dietary Phe were not considered in the clinical claim or economic model, which was based solely on blood-Phe levels. In reality, it is likely some adult patients who achieve a response to sapropterin would choose to trade-off some of the blood-Phe lowering effects with sapropterin by relaxing their Phe-restricted diet. However, the extent of this could not be elicited from the available data. For reference, the TTO study conducted by the sponsor estimated the disutility associated with a restricted diet with medical food and partly restricted diet without medical food to be 0.173 and 0.062, respectively, assuming no change in PKU symptoms. The ESC considered that normalisation of diet may be an important treatment goal. The PBAC noted that this was consistent with input received from clinicians and patients.

Comparative harms

- 6.41 The PBAC previously noted that the only statistically significant difference in adverse events reported in the trials and studies (by relative risk and odds ratio, but not risk difference) was a lower proportion of patients in the sapropterin arm of PKU-003 experiencing adverse events compared with diet alone and that the most common events reported among the trials and studies were cough, upper respiratory tract infections and nasopharyngitis (paras 6.26 & 6.27 sapropterin PSD, March 2018 PBAC meeting).

6.42 The only new safety data presented was from the 2017 data cut from PKUDOS. These results are presented in the table below.

Table 7: Most common AEs considered related to sapropterin

Proportion of patients, n (%)	Continuously treated	Previously treated	RD (95% CI)
	N = 908	N = 381	
≥ 1 drug-related AE	116 (12.8)	9 (2.4)	0.1 (0.08, 0.13)
Gastrointestinal disorders	62 (36.8)	5 (1.3)	0.06 (0.04, 0.08)
Nervous system disorders	30 (3.3)	2 (0.5)	0.03 (0.01, 0.04)
Respiratory, thoracic and mediastinal disorders	7 (0.8)	1 (0.3)	0.01 (0, 0.01)
General disorders	7 (0.8)	0	0.01 (0, 0.01)
Psychiatric disorders	15 (1.7)	0	0.02 (0.01, 0.02)
Skin and subcutaneous tissue disorders	10 (1.1)	0	0.01 (0, 0.02)
Musculoskeletal and connective tissue disorders	4 (0.4)	0	0 (0, 0.01)
Infections and infestations	4 (0.4)	0	0 (0, 0.01)
Injury, poisoning and procedural complications	2 (0.2)	0	0 (0, 0.01)

Source: Table 2.8-41, p227 of the submission. AE = adverse event
Risk differences calculated during the evaluation using Microsoft Excel.

6.43 The continuously treated group had higher rates of several AEs including gastrointestinal disorders, nervous system disorders, respiratory system disorders and mediastinal disorders. However, given the non-randomised nature of these estimates and the likeliness of important baseline differences between continuously treated and previously treated patients, it was unclear if these estimates were reflective of the comparative safety profile of sapropterin.

Benefits/harms

6.44 A summary of the comparative benefits for sapropterin plus a Phe-restricted diet compared to (placebo plus) a Phe-restricted diet is presented. No major differences were observed for harms.

Table 8 Summary of comparative benefits for sapropterin compared to placebo in all patient ages

Trial	Sapropterin n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
				Sapropterin	Placebo		
Benefits							
Proportion of patients achieving blood Phe levels <360 µmol/L							
PKU-003	13/41	1/47	14.9 (2.0, 109.1)	32	2	0.3 (0.2, 0.4)	
Change from baseline blood Phe levels							
	Sapropterin			Placebo			Mean difference: Sapropterin vs. placebo (95% CI)
	N	Mean Δ baseline blood Phe	SE	N	Mean Δ baseline blood Phe	SE	
PKU-003	41	-239	38.3	47	6	35.8	-245 (-350, -141)

Source: compiled during the evaluation

*6-week trial duration

Blue shading indicate evidence previously considered by PBAC

6.45 On the basis of direct evidence presented by the submission, after six weeks of treatment, the comparison of sapropterin plus a Phe-restricted diet compared to

(placebo plus) a Phe-restricted diet for any PKU patient (including adults, children and adolescents) resulted in:

- An additional 30% of patients achieving blood Phe levels ≤ 360 $\mu\text{mol/L}$; and
- An average reduction in blood Phe levels of 245 $\mu\text{mol/L}$.

Clinical claim

6.46 The submission described sapropterin as superior in terms of effectiveness compared with a Phe-restricted diet alone and non-inferior in terms of safety compared to a Phe-restricted diet alone.

6.47 The evaluation and the ESC considered that the claim of superiority was likely reasonable in terms of lowering blood Phe-levels, but that the magnitude and clinical significance of the benefit in adults could not be quantified based on the evidence provided as:

- The only source of comparative data on blood Phe levels was from PKU-003, which recruited patients of all ages and no specific subgroup data from adults were presented. PKU-003 was also only of short duration (six weeks) which may limit its applicability to a scenario where sapropterin usage is lifelong;
- Data from patients aged 18 to <65 years in the PKUDOS registry suggested that patients on continuous treatment with sapropterin were able to maintain blood Phe levels in the range of 360-600 $\mu\text{mol/L}$ through up to 8 years of follow-up, whereas the mean blood Phe levels were all above 600 $\mu\text{mol/L}$ in the previously treated cohort (used as a proxy for Phe restricted diet alone). However, mean baseline Phe level was lower for patients on continuous treatment compared with patients in the previously treated cohort (see Figure 1). Thus, patients in the previously treated cohort may have had more severe disease and as such any incremental benefit observed in PKUDOS was biased in favour of the group of patients who received continuous treatment with sapropterin;
- Data on the psychiatric and neurological function from the more recent data cut of the PKUDOS registry between continuously treated and previously treated patients was not specific to adults. Data from the randomised controlled trial PKU-016 also reported no statistically significant differences in ADHD-RS score or executive function between patients treated with sapropterin (n=6) compared to patients treated with placebo (n=6) who were aged >18 at baseline;
- While it was biologically plausible that a lower blood-Phe was correlated with fewer neuropsychiatric symptoms in adults, the incremental benefit associated with treatment with sapropterin was difficult to accurately quantify. While there were some statistically significant findings in observed symptoms in published studies, statistical regressions by Bilder 2016 and Burgess 2021 did not find blood Phe to be a statistically significantly correlated to neuropsychiatric symptoms or symptom scores in adult PKU patients. These studies also did not account for

alterations in dietary intake of Phe during treatment with sapropterin, and consequently it is uncertain if these outcomes would be realised in clinical practice.

- 6.48 The PBAC previously considered that ‘...the claim of superior comparative effectiveness versus either a relaxed or strict Phe-restricted diet was reasonable’ and ‘the claim of non-inferior comparative safety was reasonable’ (paras 7.10 and 7.11, sapropterin PSD, March 2018 PBAC meeting). However, the PBAC also previously considered that “the greatest benefits would be experienced in children and adolescents” in terms of clinically significant outcomes such as cognitive function and supporting growth, and acknowledged that “consumers had described a range of important benefits associated with lowering and stabilising Phe levels in adults ... but considered that the resubmission had not provided sufficient evidence to support PBS-listing in these groups” (paras 7.1 and 7.4, sapropterin PSD, March 2018 PBAC meeting). The ESC considered that the evidence presented in the current submission did not sufficiently address the key clinical issues that the PBAC raised in the adult population.
- 6.49 The PBAC considered that the claim of superior comparative effectiveness, in terms of reducing Phe levels, versus a Phe-restricted diet remained reasonable.
- 6.50 The PBAC considered that the claim of non-inferior comparative safety remained reasonable.
- 6.51 The PBAC considered that the submission did not adequately address the range of important benefits for adults associated with lowering and stabilising Phe levels. The submission also did not address the benefit of treatment in allowing patients to increase dietary protein intake. The PBAC considered that while not well-demonstrated in the clinical data, consumer input assisted in establishing the degree of benefit to patients from blood Phe-lowering treatment.

Economic analysis

- 6.52 The submission presented a cost-utility analysis using a micro-simulation model. Because the submission had not presented clinical evidence clearly addressing the PBAC’s previous concerns about the clinical meaningfulness of the benefits in adults, and the magnitude of benefit was uncertain, the evaluation and the ESC considered that a cost utility analysis may be inappropriate.
- 6.53 This model used the same structure as the concurrent pegvaliase submission model and was calculated in the same file (also refer to 5.09 pegvaliase PSD, July 2022 PBAC meeting).
- 6.54 The model structure, key inputs and rationale are presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Sapropterin in combination with Phe restricted diet versus Phe restricted diet alone
Time horizon	Lifetime (up to 100 years of age) in the model base-case vs 5 years in the key clinical studies
Outcomes	Responders and quality adjusted life years gained
Methods used to generate results	Microsimulation model using @Risk and Microsoft Excel (5,000 iterations)
Health states	'Responder', 'non-responder', 'Phe-restricted diet' and 'dead'. Responder defined as achieving either $\leq 360 \mu\text{mol/L}$ or ADHD-RS inattention subscale reduction of ≥ 5 from baseline by 2 years
Cycle length	1 week
Transition probabilities	<p><u>Response Rate</u>: Proportion of patients that achieved $\geq 30\%$ reduction from baseline in blood Phe</p> <p><u>Blood Phe progression over time</u>: Responders: change from baseline in the first week with a mean 39% decrease, range 30-49% based on a log normal distribution. Informed by post hoc analysis of 22 adult patients who reported at least one reading of $>30\%$ decrease from baseline in the first 28 days of treatment in PKUDOS, with a lower floor of 30% assumed (actual change in Phe estimated to be 0.61 (95% CI 0.51, 0.72) in post hoc analysis). Blood Phe remains constant till death. Non-responders assumed to have a decrease of $62 \mu\text{mol/L}$ for one cycle before moving back to baseline Phe from cycle 2 onwards, with no further changes in blood Phe levels in all weeks thereafter. Phe restricted diet alone: no change from baseline in the first week or in any weeks thereafter</p> <p><u>Overall survival</u> (all): General population mortality</p>
Health related quality of life	TTO direct elicitation with Swedish general population preference weights. Utility values for health states from the utility study were applied to blood-Phe categories assumed by the submission to correspond to the given health states.

Source: Table 3.1-1, p260 of the submission.

Green shading indicates components that are the same as in the pegvaliase model (Item 5.09)

- 6.55 The ESC considered that there was a lack of clinical data available to support the microsimulation approach undertaken, with a lifetime horizon. Due to the complex approach to modelling and general paucity of data, the ESC considered the economic model was highly uncertain and not informative for decision-making purposes.
- 6.56 The key differences between the pegvaliase and the sapropterin models was in the estimation of blood-Phe changes. In the sapropterin model, patients were assumed to only have one blood-Phe change (depending on if they are a sapropterin responder or not) or no change if they are treated with a Phe-restricted diet only. However, in the pegvaliase model, patients in the pegvaliase treatment arm experience a lowering of blood-Phe each cycle they remain on treatment (based on an estimated equation) until they reach a plateau of $261 \mu\text{mol/L}$ if they were responders, while patients treated with Phe-restricted diet only were assigned a once off improvement in blood-Phe of $108 \mu\text{mol/L}$ at the first cycle. Different baseline blood-Phe was also used in the two models to account for the different sources of data (PKUDOS in sapropterin and PRISM trials in pegvaliase).
- 6.57 A key issue with the sapropterin model was that no reliable clinical evidence was presented to quantify a symptomatic or clinically meaningful benefit in adult patients

initiating sapropterin or even clear benefits associated within specific Phe ranges. For example, the inputs for sapropterin response were based on a subset of 22 patients who registered at least one blood Phe reading of >30% decrease from baseline among the 117 patients in the PKUDOS registry (data extracted May 2016) who were aged 18 or older at registration.

6.58 Key drivers of the model are presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ /QALY
Baseline Phe	The model simulated baseline Phe using a lognormal distribution based on PKUDOS data.	As baseline Phe was based on a distribution in the model, probabilistic sensitivity analyses could be used. The mean ICER, by percentile of baseline Phe, ranged from \$ ² at the 75 th percentile to \$ ³ at the 99 th percentile.
Diet arm Phe improvement	Assumption of no improvement in blood-Phe for patients treated with diet only	Applying the value used in the pegvaliase model which assumed a fixed 108 µmol/L decrease from cycle 1 onwards increased the ICER by 33.65% to \$ ⁴
Utility	Patients on a partly restricted diet without medical food and no symptoms were assumed to have utility of 0.775 and patients with moderate/severe symptoms and restricted diet assumed to have utility of 0.321	Changing the utility for 120-360 µmol/L to 0.71 (corresponding to the utility for responders in the March 2018 sapropterin submission) and the utility for >1,200 µmol/L to 0.37 (corresponding to utility in uncontrolled disease in March 2018 submission) increased the ICER by 18% to \$ ⁴)

Source: Constructed during the evaluation.

The redacted values correspond to the following ranges:

¹ \$555,000 to < \$655,000

² \$255,000 to < \$355,000

³ > \$1,055,000

⁴ \$655,000 to < \$755,000

6.59 Response rate to sapropterin was not a key driver of the model as non-responders discontinue treatment after 7 days. Using a response rate of 10.4% (based on 12/115 adult patients with baseline Phe ≥ 600 µmol/L who had at least one blood-Phe measurement which was ≥ 30% lower than baseline within the first 7 days of treatment with sapropterin from PKUDOS data) increased the ICER by only 2.3% (compared with using the base case response rate of 23.5%, which was based on the response rate observed at one month). The pre-PBAC response stated there were insufficient data in the PKUDOS registry to reliably estimate the proportion of patients who achieved a response to sapropterin at one week and argued that given the rapid onset of action of sapropterin, the use of the response rate at one month as a proxy for that at one week was reasonable.

6.60 The results of the economic model are presented in Table 11.

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Table 11: Results of the stepped economic evaluation

Step and component	Saproterin	Phe restricted diet alone	Increment
Step 1: Response rate with time horizon 1 week			
Costs	\$█	\$█	\$█
Responder	23.46%	0.00	23.46%
Incremental cost/extra responder gained			\$█ ¹ /Responder
Step 2: including extrapolation, background mortality and transformation to QALYs			
Costs	\$█	\$█	\$█
QALY	9.91	8.86	1.05
Incremental cost/extra QALY gained			\$█ ² /QALY
Step 3: including continuing treatment criteria			
Costs	\$█	\$█	\$█
QALY	9.57	8.86	0.71
Incremental cost/extra QALY gained			\$█ ³ /QALY
Step 4: including all resource use			
Costs	\$█	\$█	\$█
QALY	9.57	8.86	0.71
Incremental cost/extra QALY gained			\$█ ³ /QALY

Source: Table 3.8-2, p305, of the submission

The redacted values correspond to the following ranges:

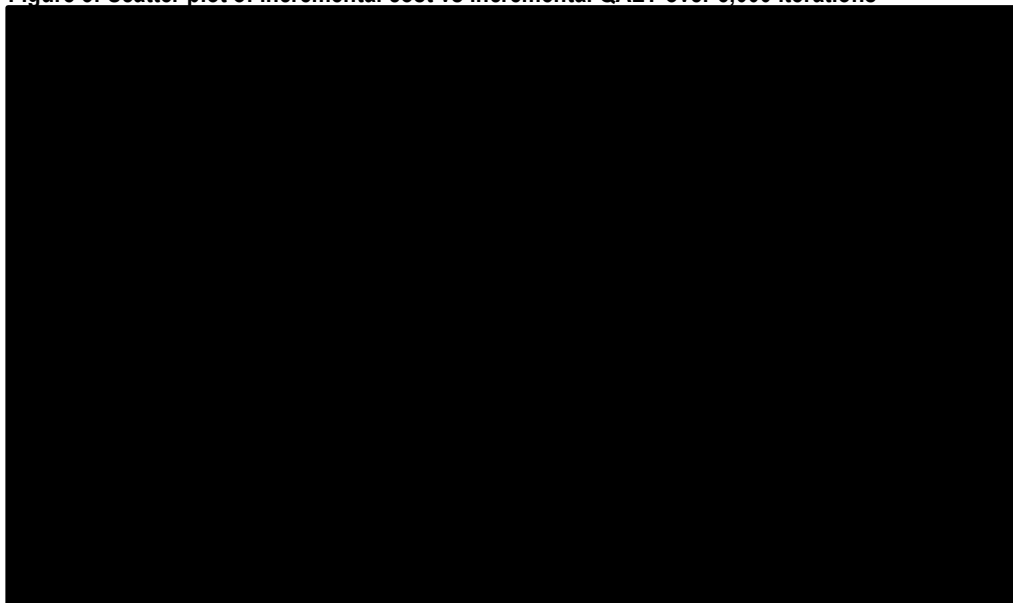
¹ \$5,000 to < \$15,000

² > \$1,055,000

³ \$555,000 to < \$655,000

6.61 The submission calculated the ICER using the mean of the costs and the mean of the QALYs from the microsimulation. However, the evaluation noted that there was substantial variation in the ICER (increasing up to > \$1,055,000/QALY) when considering the mean of all the ICERs generated in 5,000 iterations of the model. The ESC considered that this indicated the substantial variability and uncertainty in the model outcomes, due to factors such as the limitations of the underlying clinical data. This variability is also indicated in Figure 3, which shows the ICER scatterplot of the model over 5,000 iterations, with each datapoint representing the incremental cost and incremental QALY reported for one iteration (i.e. one patient).

Figure 3: Scatter plot of incremental cost vs incremental QALY over 5,000 iterations



Source: constructed during evaluation

- 6.62 The scatterplot appears to show that a substantial number of patients would have an ICER below the base case ICER as reflected by the number of data points to the right of the willingness to pay line set to the base case ICER of \$555,000 to < \$655,000/QALY. However, of the 5,000 iterations, 965 (19.3%) actually reported an incremental QALY of 0 with a cost of around \$0, as such, there were actually 4,449 patients (89%) for whom the ICER was higher than the base case ICER in the microsimulation. The large number of iterations reporting an incremental QALY gain of 0 or near 0 was consistent with the assumption that only 23.5% of patients would respond to sapropterin.
- 6.63 The submission's stated ICER of \$555,000 to < \$655,000/QALY was higher than the ICER previously calculated for adults with non-maternal PKU (\$355,000 to < \$455,000 /QALY), which the PBAC previously considered was not cost-effective (para 7.3, sapropterin PSD, November 2020 PBAC meeting).
- 6.64 In the November 2018 submission, the ICER ranged from \$45,000 to < \$55,000/QALY for patients aged less than one year to \$455,000 to < \$555,000/QALY for those aged 17 years. The ICER/QALY was \$155,000 to < \$255,000 for a patient who commenced sapropterin at birth and continued until their 18th birthday (i.e. 18-year time horizon). The ICER generally increased with age (from 0 to 17 years) because the dose of sapropterin is weight-based, however the proportion of patients who were assumed to be well controlled (in whom sapropterin is assumed to be less cost-effective) decreases after the age of 17 (para 6.37, sapropterin PSD, November 2020 PBAC meeting).
- 6.65 Table 12 presents the results of univariate sensitivity analyses.

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Table 12: Univariate sensitivity analyses conducted by submission and during evaluation (5,000 iterations)

Scenario	Incremental Cost	Incremental QALY	Incremental cost per QALY	Percentage change
Base Case	\$	0.718	\$ ¹	NA
Discount rate: 0%	\$	2.00	\$ ¹	-0.17%
Discount rate: 3.5%	\$	0.91	\$ ¹	-0.06%
Time horizon 30 years	\$	0.60	\$ ¹	+0.04%
Use March 2018 Utility *	\$	0.603	\$ ²	+18%
Response rate (10.4%) ^	\$	0.309	\$ ¹	+2.3%
Increase blood Phe decrease for diet to 108 µmol/L #	\$	0.529	\$ ²	+33.65%

* Changed utility for 120-360 µmol/L to 0.71 (corresponding to utility in responders in the March 2018 sapropterin submission) and utility for >1,200 µmol/L to 0.37 (corresponding to utility in uncontrolled disease in March 2018 submission)

^ Based on 12/115 adult patients with baseline Phe ≥600 µmol/L who had at least one blood-Phe measurement which was ≥30% lower than baseline within the first 7 days of treatment with sapropterin, consistent with the PBS indication for trialling sapropterin.

As used in pegvaliase model

Source: Table 3.9-1, p308 of the submission and constructed during evaluation

The redacted values correspond to the following ranges:

¹ \$555,000 to < \$655,000

² \$655,000 to < \$755,000

- 6.66 Probabilistic sensitivity analyses around baseline age, Phe and the assumed blood-Phe decrease for sapropterin responders indicate that baseline Phe is a key driver of the model. For example, using the 25th percentiles of baseline Phe, with a value of 839.22 µmol/L, increased the ICER by 154%.
- 6.67 The ESC considered that the univariate sensitivity analyses (which adjust assumptions using the existing model structure) did not adequately demonstrate the substantial uncertainty with the model, given the issues with the underlying data and the model structure.
- 6.68 The PBAC noted that a 30% reduction in the price of sapropterin would be required to reduce the ICER to \$355,000 to < \$455,000 /QALY and a 50% price reduction would be required to reduce the ICER to \$255,000 to < \$355,000 /QALY.

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

Table 13: Drug cost per patient for proposed drug

	Lilienstein (2018)	Model	Financial estimates
With RSA			
Mean dose	18.7 mg/kg/day	20 mg/kg/day	
Mean weight	NR	kg ^a	
Total dose	NR	mg/day	
Responsiveness testing			
Duration	7 -28 days	7 days	
Cost per patient ^b	NC	\$	
Continuing treatment			
Cost/patient/year ^c	NC	\$	
Without RSA			
Mean dose	18.7 mg/kg/day	Female	Male
		20 mg/kg/day	
Mean weight	NR	71.1 kg ^d	85.9 kg ^d
Total dose	NR	1,422	1,718mg
Responsiveness testing			
Duration	7 -28 days	7 days	
Cost per patient ^b	NC	\$	\$
Continuing treatment			
Cost/patient/year ^c	NC	\$	\$
Weighted cost/patient per year (40% male)	NC	\$	

Source: Table 26, pp 156-157 of the trial report, Section 3 workbook, sheet 3a of the utilisation-and-cost-model. Italicised values have been calculated. NC = not calculable; NR = not reported; RSA = Risk Sharing Arrangement

^a This was reflective of the existing RSA patient weight cap.

^b based on the DPMQ of \$ [REDACTED] for 500 mg of Powder for oral liquid and the DPMQ Of \$ [REDACTED] for the soluble tablet, 100 mg, each adjusted for a seven-day duration.

^c Based on the DPMQ of \$ [REDACTED] for the Powder for oral liquid, 500 mg and the DPMQ of \$ [REDACTED].

^d Based on Australian Bureau of Statistics, Australian Health Survey: First Results, 2011-2012 - Australia for body weight of persons aged 18+

6.69 The cost of sapropterin per patient per year calculated in the submission was \$ [REDACTED] including the proposed RSA, wherein expenditure caps were based on a maximum patient weight of [REDACTED] kg, a dose of 20 mg/kg and effective DPMQs of \$ [REDACTED] for the 500 mg preparation and \$ [REDACTED] for the 100 mg preparation.

6.70 The cost of sapropterin per patient per year calculated in the March 2018 PBAC PSD (paragraph 6.62) ranged from \$ [REDACTED] in the 0-year-old cohort to \$ [REDACTED] in the ≥18-year-old cohort. These costs were determined by applying the proposed effective sapropterin DPMQ (\$ [REDACTED]/100 mg) to mean weight-by-age data and a mean daily dose of 17.4 mg/kg/day. While the cost per pack was proposed to be the same as currently applies in patients aged 18 years and younger, the cost per patient would be higher in adults due to higher weight. The pre-PBAC response outlined that under the proposed risk sharing arrangement (RSA) expenditure caps are based on utilisation estimates that apply a maximum patient body weight of [REDACTED] kg. However, the PBAC noted that even with the RSA cap, the cost per patient for adult patients is higher than for paediatric patients where the required dose is lower. As noted in paragraphs 6.63 and 6.64, the ICER increases with age and the submission's stated ICER of \$555,000 to

< \$655,000/QALY in patients commencing treatment as an adult was substantially higher than the ICER for a patient who commenced sapropterin at birth and continued until 18 years (\$155,000 to < \$255,000/QALY).

- 6.71 Using undiscounted results from the economic model, it was estimated that over a mean duration of 52.67 life years, the annual cost of Phe-free supplements in the sapropterin arm was \$| (\$| in total) and in the Phe-restricted diet arm was \$| (\$| in total).

Estimated PBS usage & financial implications

- 6.72 Sapropterin was not considered by DUSC, however DUSC considered the concurrent pegvaliase item (Item 5.09), which used some of the same general epidemiological inputs. The submission took an epidemiological approach to estimating use of sapropterin.
- 6.73 Key financial inputs for the financial estimates are presented in Table 14.

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Table 14: Key inputs for financial estimates

Parameter	Value applied	Source/ Comment
Prevalence of HPA	1 per 11,226	Boneh et al. (2006). DUSC noted this was based on old data.
PKU % of HPA	98.8%	Abadie et al. (2001). DUSC noted this was based on old data.
Patients (%) under routine follow-up for PKU	70.0%	Assumption.
Patients (%) with blood Phe levels > 600 µmol/L	49.92%	Literature search. Across 21 studies included in the submission's literature search, the average proportion of patients with blood Phe levels was 49.92% (range: 28% - 100%; median: 75%). DUSC considered this was highly uncertain due to the large range in reported values across the studies.
Patients (%) achieving response to sapropterin	23.48%	Additional analyses of PKUDOS.
Body weight (kg)	Sapropterin Males: 85.9 kg Females: 71.1 kg Capped at ■ kg consistent with the proposed risk sharing arrangement	Australian Bureau of Statistics, Australian Health Survey: First Results, 2011-2012 – Australia Proposed by sponsor
Uptake rates	■% increasing by ■% each year to ■% in 2027	Assumption
Duration of treatment and persistence	Patients (%) with full year of treatment Year 1: 24.92% Year 2: 23.44% Year 3: 23.44% Year 4: 23.42% Year 5: 23.38% Year 6: 23.37%	The proportion of initiating patients who remain on treatment in each year was derived from the economic model. These proportions were generally consistent with the proportion of initial responders to sapropterin and indicate that the majority of sapropterin responders remain on treatment. However the proportion of responders remains uncertain.
Net change in the number of Phe free supplement prescriptions per patient newly initiating treatment per year	Sapropterin PKU C.10 PKU C.15 PKU C.20 Yr 1: -0.55 0.69 0.03 Yr 2: -0.55 0.70 0.03 Yr 3: -0.55 0.70 0.03 Yr 4: -0.55 0.69 0.03 Yr 5: -0.55 0.69 0.03 Yr 6: -0.55 0.69 0.03	Differences in number of prescriptions for Phe free supplements per patient newly initiating treatment in each year from economic model. It was unclear why patients treated with sapropterin would also increase the use of PKU Coolers 15 and 20. Overall, the estimates calculated a net increase in use of Phe diet supplements associated with sapropterin listing which appears counterintuitive.
Net change in the number of specialist, dietician, and blood Phe levels tests per patient newly initiating treatment per year	0.77 additional specialist visit (MBS item 116) 0.77 additional dietician visit (MBS item 10954) 0.76 additional blood Phe test (MBS item 66757)	The financial estimates assumed differences in the number of visits and tests per patient newly initiating treatment in each year. In the discussion of the economic evaluation, the submission considered an equal frequency of specialist and dietician visits across all treatments.

Source: Table 4.1-1, pp310-313 of the submission.

Green shading indicates components that are the same as in the pegvaliase submission

6.74 Table 15 presents the estimation of the eligible and treated adult population.

Table 15: Sapropterin eligible population

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Sapropterin – Prevalent eligible population						
Aged ≥ 18 years	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
HPA (0.0089%)	1	1	1	1	1	1
PKU (98.8%)	1	1	1	1	1	1
Clinic f/u (70%)	1	1	1	1	1	1
>600 µmol/L (49.9%)	1	1	1	1	1	1
Eligible population	1	1	1	1	1	1
Uptake rate	%	%	%	%	%	%
Treated patients:						
Initiating ^a	2	2	2	2	2	2
Continuing	2	2	2	2	2	2
Total treated	2	2	2	2	2	2

Source: Tables 4.2-1 and 4.2-2, pp328-9 of the submission. HPA = hyperphenylalanemia; PKU = Phenylketonuria; f/u = follow-up

^a In Year 2 to 6, initiating patients were derived by subtracting the estimated population (derived using a prevalence approach) from the previous year

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

- 6.75 It appeared that the submission did not explicitly factor in the initiation criteria that patients have not previously received sapropterin. Patients aged younger than 18 years who had previously trialled but did not achieve a response would not be eligible to trial sapropterin again after they turn 18. However, these patients would have been captured with the epidemiological approach used, therefore there was a potential to overestimate the population. The PSCR and pre-PBAC response noted that as sapropterin was only listed for the treatment of PKU in 2019, the number of patients who trialled sapropterin prior to the age of 18 years and are now 18 years or older is likely to be small.
- 6.76 The submission assumed that 70% of the adult PKU population are not under routine follow-up. Although DUSC considered that this step should be removed for pegvaliase, the PBAC noted that consultation with clinicians and the MDAA indicated that 70% may be an overestimate and clinicians estimated that it is likely that only 50% to 60% of adult patients are under routine follow-up (for example there may be limited access to metabolic clinics in some areas, some patients may have left routine care due to being unable to follow the low protein diet and/or the psychosocial impacts of PKU, or previous historical advice that routine care was not required in adulthood). This assumption would therefore overestimate the number of patients eligible for treatment.
- 6.77 The evaluation considered that uptake rates were uncertain. The evaluation considered that, on one hand, the uptake rates could be overestimated given the lack of a clear benefit in patients initiating after 18 years of age, but on the other hand could be underestimated given that sapropterin treatment generally has low risk of harms and may allow patients to increase dietary Phe intake.
- 6.78 After the first year of listing, the number of initiating patients decreased, given the large prevalent pool in Year 1. The submission subtracted the estimates of the treated

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population for each subsequent year from the estimate from the previous year. Continuing patients were estimated using persistence rates calculated in the economic model. The submission assumed 23.5% of patients were responders to sapropterin (based on 27/115 of adult patients with baseline Phe >600 µmol/L achieving a ≥ 30% reduction in blood Phe levels in the first 28 days after starting sapropterin). As noted in paragraph 6.59, the evaluation and ESC considered that there were insufficient data in PKUDOS to estimate the proportion of patients likely to achieve a response after 7 days of treatment. If response rates were as low as 10.4% (based on 12/115 adult patients with baseline Phe ≥600 µmol/L who had at least one blood-Phe measurement which was ≥30% lower than baseline within the first 7 days of treatment with sapropterin), the number of continuing patients would be overestimated. On the other hand, the response rate would be 34% (27/79) if it were based only on those patients with at least one measurement within the first 28 days (refer to Paragraph 6.31). If 34% of patients were responders to sapropterin the number of continuing patients would be underestimated.

6.79 The submission calculated the number of prescriptions based on patient weight and sex. The RSA was based on a body weight cap of 1 kg.

6.80 Table 16 presents the estimated use and financial implications for sapropterin.

Table 16: Estimated use and financial implications (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	2	2	2	2	2	2
Estimated financial implications of sapropterin						
Cost to PBS less copayments	\$3	\$3	\$4	\$4	\$4	\$4
Estimated financial implications for Phe free supplements						
Cost to PBS less copayments	\$3	\$3	\$3	\$3	\$3	\$3
Net financial implications						
Net cost to PBS (effective)	\$3	\$3	\$4	\$4	\$4	\$4
Net cost to PBS with RSA rebate	\$3	\$3	\$3	\$3	\$3	\$4
Net cost to MBS	\$3	\$3	\$3	\$3	\$3	\$3
Net cost to Government without RSA	\$3	\$3	\$4	\$4	\$4	\$4
Net cost to Government with RSA	\$3	\$3	\$3	\$3	\$3	\$4
Previous submission (March 2018: all patients – both <18 years and ≥18 years)						
Net cost to PBS	\$3	\$4	\$4	\$4	\$5	\$5

Source: attached financial spreadsheets; March 2018 sapropterin PBAC PSD

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

6.81 The total cost to the PBS of listing sapropterin was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing. After the RSA rebate was applied, the estimated cost to the PBS was \$10 million

to < \$20 million in Year 6 and a total of \$50 million to < \$60 million in the first 6 years of listing.

- 6.82 Overall, the financial estimates were likely overestimated because the number of adult patients under routine follow-up may be overestimated.
- 6.83 The evaluation considered that it was unclear why the estimates calculated a net increase in the use of Phe free diet supplements associated with sapropterin listing. It also appeared that the difference in Phe-free supplement was only assumed to apply in patients initiating sapropterin.

Financial Management – Risk Sharing Arrangements

- 6.84 The submission proposed to continue the existing risk sharing arrangement (RSA) for sapropterin whereby expenditure caps are based on utilisation estimates that apply a maximum patient body weight of █ kg, with a █% rebate on PBS expenditure exceeding the cap. The PBAC noted that this RSA would be required to manage the cost-effectiveness, noting that a maximum weight of █ kg was applied in the economic model. The PBAC had also previously considered that an RSA would be required to manage the uncertain patient population and the risk of use in patients not continuing to respond (paragraph 6.1, sapropterin PSD, November 2018 PBAC Meeting).
- 6.85 Under the existing RSA, the sponsor also rebates █% of the cost to the PBS of all sapropterin used for initial responsiveness testing. The submission did not explicitly state whether the RSA would also rebate the cost of sapropterin used for initial responsiveness testing. No further information was provided in the PSCR or pre-PBAC response.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of sapropterin for initiation in adult patients with HPA due to PKU. The PBAC was satisfied that sapropterin provides, for some patients, a significant improvement in efficacy over a Phe-restricted diet alone. The PBAC considered there was a high clinical need in a small patient population. Although difficult to quantify, the PBAC considered sapropterin use would be expected to lead to improvements in neurological function and increases in dietary protein intake. The PBAC considered the ICER was very high at the price proposed by the sponsor and considered that a substantial price reduction would be required to achieve a cost-effective listing for initiation in adult patients. Further, the PBAC considered that an RSA would be required to manage the cost-effectiveness, the uncertain patient population, and the risk of use in patients not continuing to respond.
- 7.2 The PBAC acknowledged the meaningful consumer support and engagement with regards to the submissions for sapropterin and pegvaliase (Item 5.09, which was also considered at the July 2022 PBAC meeting), including a meeting with patient and

health professional representatives held prior to the PBAC meeting. The PBAC considered that consumer input was valuable in decision-making in terms of establishing the clinical need for sapropterin by identifying and describing outcomes that were not well-captured in the clinical evidence. In addition, consultation with patients, health professionals and representative organisations assisted in consideration of the appropriate clinical place for sapropterin and pegvaliase.

- 7.3 The PBAC noted that many consumers described the current arrangements for sapropterin access as inequitable given it is only PBS-subsidised for those who initiate prior to 18 years of age.
- 7.4 The consumer input outlined the burden of current management, noting that compliance to the very onerous Phe-restricted diet is unsustainable for many patients, especially in adulthood, and frequently does not reduce blood Phe to an acceptable level. Patients reported that increased protein intake was an important outcome, enabling intake of a broader range of foods and alleviating the substantial quality of life burden associated with a severely low protein diet. In addition, patients and healthcare professionals described the neuropsychiatric symptoms associated with high Phe levels including psychosocial aspects, impacts on cognitive function and the ability to manage self-care and tasks on a daily basis. Clinicians stated that the benefits of reducing blood Phe levels in adults are significant and meaningful, with depression and anxiety scores improved and working memory and cognitive function substantially improved or returned over the longer term. Clinicians also highlighted that there is evidence that patients experience reversible changes in white matter indicative of neurodegenerative effects of raised blood Phe levels.
- 7.5 The PBAC considered that the requested place in therapy and change to the restriction, which would allow initiation of sapropterin (i.e. access to responsiveness testing and continuing treatment if response criteria are met) in patients aged 18 years and over, was appropriate.
- 7.6 The submission also requested an amendment to the administrative notes enabling patients who failed a 24-hour test prior to 1 month of age to have the opportunity to retest one additional time at >1 month of age using the 7-day responsiveness test. The PBAC considered this was appropriate and noted that the existing criteria “Patient must not have previously received PBS-subsidised treatment with this drug for this condition” would need to be amended to enable this.
- 7.7 The PBAC considered that the nominated comparator, a Phe-restricted diet alone, was the appropriate main comparator. The PBAC considered that, while sapropterin would not replace the Phe-restricted diet, it would, in practice, allow relaxation of the Phe-restricted diet in some patients.
- 7.8 With the exception of the more recent data cuts of the PKUDOS registry data, no new evidence was presented to support the comparative efficacy of sapropterin versus a Phe-restricted diet in patients aged ≥ 18 years. The PBAC had previously concluded that there was insufficient evidence to support PBS-listing in adults (paragraph 7.4,

sapropterin PSD, March 2018 PBAC meeting). The PBAC noted that there were no comparative studies presented in sapropterin-naïve adult patients and that no additional comparative evidence is likely to be forthcoming in the near term. The submission's references to published literature provided some supportive evidence regarding the benefit of controlling Phe in adults with PKU but did not provide information on the magnitude of any benefits of sapropterin in terms of neuropsychiatric symptoms in adults. Overall, the PBAC considered the incremental benefit of sapropterin in adults was not well-captured in the clinical evidence presented, particularly for patients commencing sapropterin in adulthood, and especially in terms of clinically meaningful health outcomes such as the effect on neurological function.

- 7.9 The PBAC considered that the claim of superior comparative effectiveness and non-inferior comparative safety versus a Phe-restricted diet remained reasonable. However, the PBAC considered that the submission did not adequately address the range of important benefits for adults associated with lowering and stabilising Phe levels or of enabling increased dietary protein intake. The PBAC considered that while not well-demonstrated in the clinical data, consumer input assisted in establishing the degree of benefit to adult patients from blood Phe-lowering treatment.
- 7.10 The submission presented a cost-utility analysis using a micro-simulation model. The PBAC considered that the cost-utility analysis was limited because the submission did not present clinical evidence clearly addressing the clinical meaningfulness of the benefits in adults, and the magnitude of benefit was uncertain. Overall, the PBAC considered that there was a lack of clinical data available to support the microsimulation approach undertaken, particularly with a lifetime horizon. The PBAC agreed with the ESC that due to the complex approach to modelling and general paucity of data, the economic model was highly uncertain and noted the ESC's advice that the model was not informative for decision-making purposes. The PBAC recalled that it had previously considered that the model submitted in March 2018 was unreliable in terms of estimating cost-effectiveness in the adult population (para 7.12, sapropterin PSD, March 2018 PBAC meeting).
- 7.11 Further, the PBAC noted that the sponsor had proposed the same cost per pack as currently applies in children (and all patients). As dosing is weight-based (with an RSA based on expenditure caps that assume a maximum patient weight of 1 kg), the cost per patient would generally be higher in an adult patient than a paediatric patient. The PBAC considered this was not appropriate as the clinical benefit is less certain in adults, reiterating its previous consideration that the benefits of sapropterin in terms of improved neurological function were likely to be greatest during the period of neurological development for children and adolescents (para 7.2, sapropterin PSD, March 2018 PBAC meeting). The PBAC also noted that use in the population under the age of 18 years was associated with a substantially lower ICER, as outlined in paragraphs 6.63 and 6.64.
- 7.12 Overall, the PBAC considered there were substantial limitations with both the model

provided with the current submission and the previous model considered at the March and November 2018 meetings and, further, that it was not reasonable for the cost per patient to be the same in an initiating adult patient as in the existing listing which includes paediatric and maternal patients. Using either model, the PBAC considered the ICER was very high at the price proposed by the sponsor and considered that a substantial price reduction would be required to achieve a cost-effective listing for adult patients. In this context, the PBAC considered that in patients commencing treatment as an adult, a 50% reduction in the price of sapropterin would be required. The PBAC noted this would reduce the ICER to \$255,000 to < \$355,000/QALY using the model provided with the current submission. The PBAC considered that with this reduction in price, the ICER, though very high and uncertain, would be acceptable in the context of the high clinical need, high burden of disease and small patient population where equity of access is an additional consideration.

- 7.13 The PBAC noted that the submission estimated that the revised listing would result in approximately < 500 additional adult patients receiving sapropterin each year from years 2-6 after listing. This is in addition to around 300 patients per year for the existing sapropterin listings. Overall, the PBAC considered that the financial estimates were likely overestimated and should be revised to reduce the number of adult patients under routine follow-up from 70% to 55%. The PBAC considered there was also uncertainty regarding the proportion of responders and the likely uptake rates, but considered that no alternative estimates had been presented that were likely to be more reliable than those used in the submission.
- 7.14 The submission proposed to continue the existing risk sharing arrangement (RSA) for sapropterin whereby expenditure caps are based on utilisation estimates that apply a maximum patient body weight of █ kg. The PBAC considered that increases to the RSA caps in line with the revised financial estimates described in paragraph 7.13 and using the revised price described in paragraph 7.12 would be appropriate, with a █% rebate for utilisation above the agreed estimates in keeping with the existing RSA for sapropterin.
- 7.15 The PBAC considered that, consistent with the existing RSA, a █% rebate should also apply to the cost to the PBS of all sapropterin used for initial responsiveness testing.
- 7.16 In terms of flow-on restriction changes, the PBAC noted the existing listing for Maternal HPA due to PKU will no longer be required once the restriction includes responsiveness-testing and ongoing treatment in adult patients.
- 7.17 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for sapropterin:
- a) The treatment is expected to provide a substantial and clinically relevant

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improvement in efficacy, over alternative therapies. Although difficult to quantify, the PBAC considered sapropterin use would be expected to lead to improvements in neurological function and increases in dietary protein intake.

- b) The treatment is expected to address a high and urgent unmet clinical need for adult patients.
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:

Recommended

8 Recommended listing

8.1 Pending agreement on price, amend existing listings as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SAPROPTERIN					
sapropterin dihydrochloride 100 mg soluble tablet, 30	11676M	1	30	0	Kuvan
sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	11971C	1	30	0	Kuvan
Request an appropriate maximum quantity (with the number of packs being a whole number) to provide 7 days treatment duration per dispensing, based on dosing no greater than 20 mg/kg per day.					
Edit Restriction Summary: 8898 / Treatment of Concept: 8898					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online/PBS Authorities system)					
Indication: Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)					
Treatment Phase: Initial treatment - responsiveness testing					
Treatment criteria:					
Must be treated by a metabolic physician					
Clinical criteria:					
Patient must not have previously received PBS subsidised treatment with this drug for this condition					
Patient must be untreated with this drug; or					
Patient must have completed prior responsiveness testing on only 1 occasion – this occurred when the patient was less than 1 month of age, but this benefit is for a second attempt at responsiveness testing in a patient aged at least 1 month old					
AND					
Clinical criteria:					
Patient must have a baseline blood phenylalanine level above 360 micromole per L and be less than one month of age; or					
Patient must have a baseline blood phenylalanine level above 600 micromole per L and be more than one month of age					

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	AND
	Clinical criteria:
	The treatment must be for the purpose of initial responsiveness testing for a period of 24 hours in a patient less than one month of age; or
	The treatment must be for the purpose of initial responsiveness testing for a period of 7 days in a patient aged more than one month
	Population criteria:
	Patient must be under 18 years of age
	Prescribing Instructions: Dietary phenylalanine intake must be maintained at a constant levels.
	Prescribing Instructions: 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.
	Administrative Advice: Special pricing arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: Patient will be eligible for a maximum of one PBS subsidised prescription as initial therapy to enable their response to treatment with sapropterin to be assessed.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SAPROPTERIN					
sapropterin dihydrochloride 100 mg soluble tablet, 30	11691H	6	180	5	Kuvan
sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	11983Q	1	30	5	Kuvan

Edit Restriction Summary 8817 / ToC: 8926	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Administrative Advice: Special pricing arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Indication: Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: First continuing treatment
	Treatment criteria:
	Must be treated by a metabolic physician; or
	Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment under the Initial - responsiveness testing restriction with this drug for this condition;
	AND
	Clinical criteria:
	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

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	Prescribing Instructions: Blood phenylalanine levels must be based on measurements taken during stable periods of the condition.
	Prescribing Instructions: Dietary phenylalanine intake must be maintained at a constant level.
Edit Restriction Summary 10354 / ToC: 10364	
	Indication: Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: Subsequent continuing
	Treatment criteria:
	Must be treated by a metabolic physician; or
	Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction;
	AND
	Clinical criteria:
	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
<i>The following restrictions attached to the powder for oral liquid (11983Q) relating to maternal HPA/PKU are unaltered and therefore not displayed here:</i>	
Restriction Summary 11982 / ToC: 11836	
Indication: Maternal hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)	
Treatment Phase: Pre-conception through to when pregnancy first becomes known	
Restriction Summary 11837 / ToC: 11960	
Indication: Maternal hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)	
Treatment Phase: Existing pregnancy to birth	

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

BioMarin would like to thank the PBAC for its recognition of the high unmet need in the adult PKU population and looks forward to finalising the listing.