

## **7.05 SAPROPTERIN,**

**Tablet (soluble) containing sapropterin dihydrochloride  
100 mg,  
Kuvan<sup>®</sup> ,  
BioMarin Pharmaceutical Australia.**

### **1 Purpose of application**

- 1.1 Section 85, Authority required (in writing) listing for sapropterin for the treatment of hyperphenylalaninaemia (HPA) caused by phenylketonuria (PKU) who have previously been shown to be sapropterin-responsive. The first submission (requesting listing for both PKU and BH4 deficiency) was considered at the November 2011 PBAC meeting.
- 1.2 The basis for the requested listing was a cost-utility analysis compared with a strict / relaxed / abandoned phenylalanine (Phe)-restricted diet and Phe-free supplements.

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

Component	Description	
Population	Patients with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) and who are sapropterin-responsive. The resubmission described two populations: <ul style="list-style-type: none"> <li>• Those with poorly controlled phenylalanine (Phe) blood levels; and</li> <li>• Those with well controlled Phe blood levels.</li> </ul> The PBAC considered that these do not represent two distinct sub-populations as patients would cycle between the two groups.	
Intervention	Based on the two described populations, the nominated interventions were:	
	<b>Poorly controlled Phe blood levels:</b>	Sapropterin 5-20 mg/kg/day + usual Phe-restricted diet with Phe-free protein supplements (ie, an abandoned or relaxed diet, rather than a strict diet).
	<b>Well controlled Phe blood levels:</b>	Sapropterin 5-20 mg/kg/day + Phe-restricted diet with Phe-free protein supplements (ie, a strict diet)
Comparator	Based on the two described populations, the nominated comparators were:	
	<b>Poorly controlled Phe blood levels:</b>	Placebo (PBO) + their usual Phe-restricted diet with Phe-free protein supplements (ie, a relaxed diet)
	<b>Well controlled Phe blood levels:</b>	Phe-restricted diet with Phe-free protein supplements (ie, a strict diet)
Outcomes	Based on the two described populations, the nominated outcomes were:	
	<b>Poorly controlled Phe blood levels:</b>	Change in blood Phe levels
	<b>Well controlled Phe blood levels:</b>	Change in dietary restrictions (Phe-intake and Phe-supplements)
The PBAC considered that there were issues with the nominated comparators and outcomes as they were based on sub-populations that did not reflect the Australian population.		
Clinical claim	Based on the two described populations, the clinical claims made by the resubmission were:	
	<b>Poorly controlled Phe blood levels</b>	Sapropterin in combination with the usual Phe-restricted diet is superior in terms of reducing blood Phe levels than placebo plus the usual Phe-restricted diet alone
	<b>Well controlled Phe blood levels</b>	Sapropterin in combination with a Phe-restricted diet is superior in terms of increasing dietary Phe intake compared with a strict Phe-restricted diet

Source: Table 1-1, p21 of the resubmission and Sections 1 and 2 of the resubmission.

## 2 Requested listing

- 2.1 The resubmission requested PBS-listing for the treatment of all sapropterin responsive patients, irrespective of age or phenylalanine (Phe) blood levels. This differed to the previous submission which specified different qualifying Phe levels for different age groups. The November 2011 PBAC had stated that it was unclear whether these were clinically appropriate and how they would relate to clinical practice.
- 2.2 The resubmission had proposed a continuing restriction only. To address concerns raised in the commentary, the Pre-Sub-Committee Response (PSCR) also proposed an initial restriction, which is also outlined below.

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Table 2: Key elements of the requested listing – initial (as proposed in PSCR)

Name, Restriction, Manner of administration and form	Max Qty (packs)	Max. Qty (unit)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SAPROPTERIN DIHYDROCHLORIDE 100MG, SOLUBLE TABLETS, PACK OF 30	1	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Kuvan® BioMarin Pharmaceutical Australia Pty Ltd

Initial restriction (proposed in PSCR)	
Category/Program:	General Schedule Section 85
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Episodicity:	Chronic
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Initial
Restriction:	Section 85 (Authority Required in Writing)
Treatment criteria:	Must be treated by a metabolic physician or a medical practitioner experienced in the treatment of phenylketonuria (PKU)
Clinical criteria:	Patient must have hyperphenylalaninemia (HPA) due to phenylketonuria (PKU). AND Patient must have previously been shown to be responsive to sapropterin.
Prescriber criteria:	The authority application must be in writing and include: 1. Documented confirmed diagnosis of PKU 2. Documented response to sapropterin At the time of authority application, medical practitioners should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose and weight of the patient, for one month of treatment. Up to a maximum of 5 repeats will be authorised.
Continuing restriction (proposed in resubmission and updated in PSCR)	
Category/Program	Section 85
Episodicity:	Chronic
Condition:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Continuing
Restriction:	Section 85 (Authority Required in Writing)
Treatment criteria	Must be treated by a metabolic physician or a medical practitioner experienced in the treatment of phenylketonuria (PKU)
Clinical criteria:	Must have previously been issued with an authority prescription for this drug for this condition AND Patient must have demonstrated blood phenylalanine levels within the target range, or a maintenance of blood phenylalanine levels achieved at sapropterin responsiveness testing.
Prescriber Instructions:	The authority application must be in writing and include documentation of blood phenylalanine levels within the target range, or a maintenance of blood phenylalanine levels achieved at sapropterin responsiveness testing.  At the time of authority application, medical practitioners should request the appropriate number of packs to provide sufficient drug, based on the prescribed dose and weight of the patient, for one month of treatment. Up to a maximum of 5 repeats will be authorised.

Source: Table 1-10 & 1-11, p39 & 41 of the resubmission

- 2.3 A special pricing arrangement was proposed with a published price and an effective price, whereby the sponsor would pay a rebate to the Government.
- 2.4 The previous submission (considered at the November 2011 PBAC meeting) requested an additional initial indication (BH4 deficiency which has since been PBS-

listed). The previous submission requested a Section 100 (Highly Specialised Drugs Program) listing, while the resubmission requested a Section 85 (general schedule) listing. Further, the previous submission requested a DPMQ of \$ [REDACTED], while the DPMQ requested in the resubmission, of \$ [REDACTED], was [REDACTED] % lower.

2.5 During evaluation, an issue that was identified with the requested listing (proposed in the resubmission), was that an initial treatment listing was not requested, and therefore initial response may not be auditable. Additionally, there were no specifications indicating how, or if, a continued response would be measured once patients have begun continuing treatment. To address these issues, the PSCR provided the following additional information:

- Initial supply: The PSCR proposed an initial restriction (outlined above), however the sponsor maintained that it would “provide access to sapropterin for the purpose of sapropterin responsiveness testing as requested by each patient’s metabolic physician who would conduct the testing and determine sapropterin responsiveness at their usual PKU clinics”.
- Initial response: The PSCR stated that, for sapropterin responsiveness testing, it envisaged that clinicians would be guided by the recommended dosing regimen from the Product Information: seven days of sapropterin 10 mg/kg which can be extended up to one month with sapropterin 20 mg/kg.
- Responsiveness testing: To determine initial response, the PSCR referred to the Product Information, which defined a satisfactory response as a  $\geq 30\%$  reduction in blood Phe levels or attainment of therapeutic blood Phe goals as defined for an individual patient by the treating physician. The PSCR further noted that the sapropterin clinical trials defined sapropterin responsiveness as a  $\geq 30\%$  reduction in blood Phe levels, but also considered that clinical judgement may be relevant (e.g. if Phe levels are elevated due to illness or dietary overcorrection). The PBAC considered that the resubmission had not provided sufficient evidence regarding: the processes for responsiveness testing; that the treatment effect varies between individuals; that this variation cannot be determined based on genotyping or clinic-pathological features alone; and that not all individuals meet the treatment targets. Further, while the PBAC noted that a reduction in 30% in Phe was the cut-off used for determining initial responsiveness in some clinical studies, the PBAC considered that the resubmission had neither described the underlying basis for this target, nor whether the 30% reduction was relevant regardless of baseline Phe levels.
- To make attainment of an initial response auditable, the PSCR proposed that clinicians would be required to provide documentation of sapropterin responsiveness. That is, the PSCR’s proposed initial PBS restriction included the prescriber instruction that “The authority application must ... include ... documented response to sapropterin”. Though not stated in the proposed restriction, the PSCR proposed that blood Phe measurements would be required at baseline (prior to responsiveness testing) and when response is achieved (i.e.

after up to 28 days).

- Continuing response: For continuing access, the PSCR proposed that evidence of sustained benefit would need to be provided every six months. That is, the proposed continuing restriction included the instruction that “the authority application must ... include documentation of blood phenylalanine levels within the target range, or a maintenance of blood phenylalanine levels achieved at sapropterin responsiveness testing”.

- 2.6 DUSC was concerned that the revised initial restriction proposed in the PSCR did not address that determination of sapropterin response lies outside the PBS and is clinically subjective; and that response to sapropterin was not adequately defined.
- 2.7 DUSC noted that grandfathering arrangements were not proposed. DUSC considered that sapropterin may be available for some PKU patients via hospital pharmacy funding arrangements; however the extent of this is unclear.
- 2.8 The ESC considered that a number of issues with the proposed restriction remained, but that these could only be resolved subsequent to the other clinical issues raised.

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

### **3 Background**

#### ***Registration status***

- 3.1 Sapropterin was TGA registered on the 21<sup>st</sup> October 2010 for “the treatment of HPA in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency”.

#### ***Previous PBAC consideration***

- 3.2 Table 3 summarises the key outstanding matters from the previous PBAC consideration.

**Table 3: Summary of outstanding matters of concern**

Component	Matter of concern (November 2011)	How the resubmission addresses it
Comparator	The PBAC did not accept the nominated comparator of placebo plus standard management with a Phe-restricted diet and dietary supplements because of the uncertainty regarding whether sapropterin would replace, or be used as an adjunct, to diet. A more appropriate comparator would have been “standard management with a Phe-restricted diet in combination with Phe-free protein supplements as the same therapeutic outcome (reduction in blood Phe levels) is also achieved by adherence to a Phe-restricted diet in combination with Phe-free protein supplements” (pg 7, Nov 2011 PSD)	The resubmission split the patient population into two sub-groups based on Phe blood level control, each with a different comparator. Patients with ‘poorly-controlled’ Phe levels have a placebo + a relaxed or abandoned Phe-restricted diet comparator. Patients with ‘well-controlled’ Phe levels have a strict Phe-restricted diet comparator.
Requested Restriction	“The PBAC was unclear whether the proposed restrictions for treatment of HPA with PKU, which are split by age group with different qualifying Phe levels, were clinically appropriate and how they would relate to clinical practice” and were uncertain about “clinical relevance of a 30% reduction in baseline levels” (pg 8, Nov 2011 PSD).	Proposed restriction was for patients who are sapropterin responsive (sponsor proposed that it would provide access to sapropterin for responsiveness testing). Not restricted by age or blood Phe-control. The restrictions proposed in the PSCR did not include specific thresholds for defining initial or continuing response.
Evidence	“There were no data to suggest whether treatment with sapropterin allows meaningful changes in dietary restrictions for some patients over the long term, or in patients uncontrolled using a Phe-restricted diet” (p8, Nov 2011 PSD)..	Longer-term data was presented showing continued increased Phe tolerance among those well controlled. No data reported for dietary changes among those uncontrolled.
Utility values	Many of the utility values used in the model appeared implausible and associated with uncertainty (pg 8, Nov 2011 PSD).	Utility values from evaluator-conducted sensitivity analyses from the previous submission were used, however the derivation of these values was unclear.
Financial estimates	Patients aged over 40 years were inappropriately excluded, and estimates did not “account for patients continuing PBS treatment with sapropterin via grandfathering which is inconsistent with the requested listing” (pg 8, Nov 2011 PSD).	Financial estimates excluded patients aged >51 in 2017. No grandfathering was proposed.

Source: Sections 1, 2 3 and 4 of the resubmission

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

## 4 Population and disease

- 4.1 PKU is a rare inborn error of metabolism that leads to HPA whereby patients experience elevated levels of the essential amino acid Phe in the blood due to a poorly-functioning enzyme (phenylalanine hydroxylase). There is a spectrum of disease severity related to the residual activity of the defective enzyme.
- 4.2 If untreated in neonates and children, high Phe blood levels can lead to mental retardation, neurocognitive deficits, behavioural abnormalities, seizures and other serious neurological complications. By around 10 to 12 years of age, IQ appears to be fixed and remains stable independent of Phe levels. In adolescents and adults, high Phe blood levels can lead to subtle, reversible effects on neurocognition (Lachmann, 2011)<sup>1</sup>.

<sup>1</sup> Lachmann, R. (2011). Sapropterin Hydrochloride: Enzyme Enhancement Therapy for Phenylketonuria. Therapeutic

- 4.3 The resubmission stated that newborn screening and dietary treatment commencement shortly after birth has eliminated the effects of severe intellectual disability for people with PKU.
- 4.4 Current management of PKU involves regulating dietary Phe-intake through: restricting natural protein intake; taking Phe-free amino acid, vitamin and mineral supplements to meet protein and non-protein requirements; and consuming low-protein food to meet energy requirements. The degree of Phe restriction varies and depends on factors such as the severity of PKU, age and growth rate.
- 4.5 The resubmission stated the current dietary management of PKU is difficult to adhere to because of the restrictions on the type and amount of food intake. It stated that a Phe-restricted diet requires a considerable time commitment and includes weighing foods, keeping records of Phe intake and preparing special low Phe foods.
- 4.6 The PBAC noted that the PKU diet mainly comprises synthesised low protein foods, with restrictions extending to wheat, rice and other grains, nuts, soy and some vegetables and fruits (e.g. bananas, avocados and broccoli). The PBAC noted that the daily protein allowance may be as low as 6 grams in some patients, which is equivalent to one avocado.
- 4.7 Guidelines generally recommend maintaining blood Phe levels  $\leq 360 \mu\text{mol/L}$ , although target levels may vary. For example, the Australian guidelines state that in patients over 12 years of age, an informed decision to accept Phe levels above  $360 \mu\text{mol/L}$  may be appropriate in some cases. On the other hand, children, pregnant women and pre-conception women with PKU are often required to maintain their blood Phe-levels at a lower targeted range than adolescents and adults with PKU.
- 4.8 Sapropterin is proposed as a first-line therapy in conjunction with a Phe-restricted diet and Phe-free amino acid supplements for those individuals with a diagnosis of PKU and neonatal/untreated Phe blood levels  $\geq 360 \mu\text{mol/L}$  who are sapropterin-responsive.
- 4.9 Sapropterin acts by enhancing the activity of the defective enzyme (phenylalanine hydroxylase) allowing Phe to be more effectively metabolised. It acts as a cofactor, and 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 mutant 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. (Lachmann, 2011)

- 4.10 The aim of sapropterin therapy is to reduce blood Phe levels and/or improve an individual's ability to tolerate higher amounts of Phe in the blood (i.e. maintain blood Phe levels within the target therapeutic range while increasing dietary intake of Phe).

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

## 5 Comparator

- 5.1 The nominated comparators changed since the previous submission (see Table 3) and were:

- 'placebo + a relaxed or abandoned diet' for individuals with poorly-controlled blood Phe-levels. The resubmission considered that sapropterin was likely to result in a reduction in blood Phe levels in these patients; and
- 'a strict Phe-restricted diet' for those with well-controlled blood Phe levels. The resubmission considered that sapropterin was likely to allow a liberalisation of the diet (increased intake of natural protein) in these patients. Note that the Phe-diet relates to restricted Phe dietary intake and to Phe-free supplements.

- 5.2 The resubmission noted that the two patient groups were not mutually exclusive, with most patients cycling between the groups because of the difficulty in maintaining a strict low Phe diet. Further, the proportion of patients with well-controlled blood Phe levels decreases with age as compliance with a strict diet decreases.

- 5.3 The PBAC considered that these do not represent two distinct sub-populations sufficient to justify the use of different comparators and outcomes, particularly given that patients would likely cycle between the two groups. Further, there was uncertainty in segregating patients into either benefiting only from reductions in blood Phe-levels or only from reductions in dietary restrictions.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (919), health care professionals (42) and organisations (4) via the Consumer Comments facility on the PBS website.

- 6.3 Representatives of the PBAC met with representatives of the Metabolic Dietary Disorders Association (MDDA) prior to the PBAC meeting. The following is a summary of the perspectives presented to the PBAC representatives:

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- PKU affects the quality of life of patients and their families, impacting on a patient's cognitive function, mental health and social inclusion. The patients and their carers outlined the complex dietary requirements which are particularly difficult to manage in social situations, at school and at work.
- The patient representatives outlined that protecting brain function is the primary objective of any PKU treatment. High Phe levels can lead to irreversible neurological damage in babies and children, and subtle reversible effects on neurological function in adults.
- The patient representatives acknowledged that not all patients with PKU would respond to sapropterin, and those who do respond would still need to adhere to a highly restricted diet (although more liberal than without sapropterin). The patient representatives outlined that, in responsive patients, sapropterin would:
  - lead to improvements in neurological function, which may reduce fluctuations in mood, reduce anxiety and improve concentration. The patient representatives outlined that this may enable patients to study, maintain stable employment and healthy relationships, and aid compliance to diet;
  - minimise the health impacts associated with inadequate dietary intake of natural protein and nutrients which include impaired growth, osteoporosis, diabetes and obesity (as low Phe foods are generally high in calories and sugar);
  - minimise the fluctuations in Phe levels during periods of protein consumption or intercurrent illness (e.g. common cold or hayfever), which may improve neuropsychological outcomes;
  - enable more flexibility in a patient's diet which would facilitate eating in social situations such as at childcare and school, on school trips and at restaurants. It would also reduce worry and anxiety about diet;
  - reduce the need for special formula and complex multi-vitamin regimens. The special formula needs to be consumed at fixed intervals which can be intrusive on daily life; and
  - help patients maintain their blood Phe closer to the levels recommended in guidelines.
- The patient representatives highlighted that PKU is particularly difficult to manage during pre-conception and pregnancy. Lower blood Phe levels must be maintained to reduce the risk of deformities or miscarriage; for some patients this means they can only consume synthesised foods during this time. The patient representatives also outlined that sapropterin may enable some babies with PKU to be breastfed.
- The patient representatives considered that all patients with HPA due to PKU should have the opportunity to be tested for sapropterin responsiveness,

regardless of age or Phe levels, as all patients have potential to benefit from sapropterin therapy.

- The patient representatives outlined that there is no distinction between patients whose blood Phe levels are well-controlled and those whose levels are poorly-controlled, with most patients cycling between the groups.

6.4 The PBAC also noted correspondence from a clinician describing their centre’s extensive experience with sapropterin. The correspondence stated that around 20% to 30% of patients with PKU (with blood Phe >400 micromol/L) respond to sapropterin and there are clear biological factors for determining responsiveness. As part of the centre’s protocol for determining responsiveness, babies diagnosed with PKU are administered a sapropterin load, with Phe and tyrosine levels monitored regularly for the following 24 hours. In patients who are responsive, sapropterin is commenced once solids are introduced. Patients then undergo regular, lifelong monitoring of their blood Phe levels and also their Phe to tyrosine ratio.

6.5 The correspondence also noted that, in responsive patients, sapropterin is effective in reducing the requirements for strict adherence to low Phe formulae and foods, which can significantly impact quality of life, particularly in teenagers. The correspondence re-affirmed the views presented by the patient representatives, particularly highlighting that sapropterin can: help stabilise Phe levels which may lead to improved neuropsychological outcomes (although it was acknowledged that this has not been unequivocally confirmed); and increase tolerance to natural protein which leads to improvements in body composition.

### Clinical trials

6.6 Table 4 outlines the included studies by outcome reported. The key outcome for the sub-group of patients with poorly controlled Phe (on a ‘relaxed/abandoned’ diet) was changes in Phe blood levels; while the key outcome for patients with well controlled Phe (on a strict diet) was change in dietary Phe intake.

**Table 4: Trials and studies by reported outcome**

Response	Phe Blood levels		Dietary Phe intake		Long-term data		
≥30% reduction in blood Phe levels	Change in blood Phe levels from baseline to endpoint		Change in dietary Phe intake from baseline to endpoint		Change in dietary Phe intake		
PKU-001, N=490	OL, SA	PKU-003, N=88	DB, R	PKU-006 (Pt 2), N=45	DB, R	PKUDOS; N=715	Registry
EMR_700773_510, N=90		PKU-006 (Pt 2), N=45	DB, R	SPARK, N=56	OL, R	KAMPER; N=575	Registry
ENDURE, N=59		PKU-004, N=80	OL, SA	PKU-015 (Pt 2), N=65	OL, SA		
PKU-006 (Pt 1), N=90		PKU-008, N=111	OL, SA	KOGNITO, N=26	OL, SA		
PKU-015 (Pt 1), N=80							

DB=double blind; OL=open-label; Pt=Part; R=randomised; SA=single arm

Source: Figure 2-3, p54 of the resubmission

6.7 Trials and studies shaded in grey in the table above and throughout this section are those that are new to the resubmission. All other trials and studies were considered by the PBAC in the submission considered at the November 2011 meeting.

6.8 Details of the trials presented in the resubmission are provided in Table 5.

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**Table 5: Trials and associated reports presented in the resubmission**

<b>Trial/Study</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
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	22 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	22 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	11 December 2008
	Burton et al. (2007) 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 30:700–707
EMR_700773_510	A phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in patients of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels	25 November 2013
	Addendum to Clinical Trial Report: A phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in patients of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels	24 July 2014
	Bushueva et al. (2014) Open, Non-Comparative Phase III Clinical Study to Evaluate the Efficacy and Safety of Sapropterin in Patients with Phenylketonuria and Hyperphenylalaninemia.	Annals of the Russian Academy of Medical Sciences. 7–8: 69–77
ENDURE	ENDURE: A Phase IV, Prospective, Open-label, Uncontrolled, Multi-Centre Cohort Trial to Assess the Responsiveness of Subjects with Phenylketonuria (PKU) to Treatment with Kuvan® 20 mg/kg/day for 28 Days.	23 April 2013
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	5 December 2006
	Levy et al. (2007) Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study	Lancet 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	16 March 2007
	Lee et al. (2008) Safety and Efficacy of 22 Weeks of Treatment with Sapropterin Dihydrochloride in Patients with Phenylketonuria.	American Journal of Medical Genetics 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	19 April 2010
	Burton et al. (2011) Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: Results of a phase 3b study.	Molecular Genetics and Metabolism 103: 315–322
PKU-006	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin (sapropterin dihydrochloride) 20 mg/kg/day to Increase Phenylalanine Tolerance in Phenylketonuric Children on a Phenylalanine-restricted Diet	2 April 2007

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<b>Trial/Study</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
	Potential reduction in the cost of medical foods and Phe-free formulas Trefz et al. (2009) Efficacy of Sapropterin Dihydrochloride in Increasing Phenylalanine Tolerance in Children with Phenylketonuria: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study.	28 August 2007 Journal of Pediatrics 154: 700-707
SPARK	A Phase IIIb, Multicentre, Open-Label, Randomized, Controlled Study of the Efficacy, Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients <4 Years Old Muntau et al. (2017) Efficacy, safety and population pharmacokinetics of sapropterin in PKU patients <4 years: results from the SPARK open-label, multicentre, randomized phase IIIb trial	25 June 2014  Orphanet Journal of Rare Diseases 12:47
PKU-015	A Phase 3b Open-Label Study to Evaluate the Effect of Kuvan® on Neurocognitive Function, Maintenance of Blood Phenylalanine Concentrations, Safety, and Population Pharmacokinetics in Young Children with Phenylketonuria Longo et al. (2015a) Long-term developmental progression in infants and young children taking sapropterin for phenylketonuria: a two-year analysis of safety and efficacy.	26 June 2013  Genetics in Medicine 17: 365-373
KOGNITO	A Phase IV Open-Label, Single-Cohort Study of the Long-Term Neurocognitive Outcomes in 4 to 5 Year-Old Children with Phenylketonuria Treated with Sapropterin Dihydrochloride (Kuvan®) for 7 Years	13 January 2016
PKUDOS	Longo et al. (2015b) Long-term safety and efficacy of sapropterin: The PKUDOS registry experience. Grange et al. (2014) Sapropterin dihydrochloride use in pregnant women with phenylketonuria: An interim report of the PKU MOMS sub-registry	Molecular Genetics and Metabolism 114: 557–563 Molecular Genetics and Metabolism 112: 9–16
KAMPER	Kuvan® Adult Maternal Paediatric European Registry (KAMPER) (7th Interim report)	9 June 2017

Source: Table 2-3, pp51-53 of the resubmission

6.9 The key features of the trials and studies are summarised in Table 6. None of these studies were used in the economic evaluation.

Table 6: Key features of the included evidence

Trial/Study Dose of sapropterin	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Relevance in submission
<b>Sapropterin + diet versus diet alone</b>						
PKU-003 10 mg/kg/day	88	R, DB 6 weeks	Low	Uncontrolled	Reduction blood Phe	Efficacy in poorly- controlled pts
PKU-006 (Part 2); 20 mg/kg/day	45	R, DB 6 weeks	Low	Controlled	Phe tolerance Reduction blood Phe	Efficacy in well controlled pts
SPARK 10-20 mg/kg/day	56	R, OL 26 weeks	Moderate	Controlled	Phe tolerance	Efficacy in well controlled pts
<b>Single –arm, open-label studies</b>						
PKU-001 10 mg/kg/day	490	SA, OL 8 days	NA	Uncontrolled	Response rate	Determination of response rate
EMR_700733_510 20 mg/kg/day	90	SA, OL 8 days	NA	Uncontrolled	Response rate	Determination of response rate
ENDURE 20 mg/kg/day	59	SA, OL 28 days	NA	Uncontrolled	Response rate	Determination of response rate
PKU-006 (Part 1) 20 mg/kg/day	90	SA, OL 8 days	NA	Controlled	Response rate	Efficacy in well controlled pts
PKU-015 (Part 1) 20 mg/kg/day	80	SA, OL 28 days	NA	Controlled	Response rate	Determination of response rate
PKU-004 5-20 mg/kg/day	80	SA, OL 22 weeks	NA	Uncontrolled	Reduction blood Phe	Efficacy in poorly- controlled pts
PKU-008 5-20 mg/kg/day	111	SA, OL 3 years	NA	Uncontrolled / Controlled	Reduction blood Phe	-
PKU-015 (Part 2) 10-20 mg/kg/day	65	SA, OL 2 years	NA	Controlled	Phe tolerance	-
KOGNITO 5-20 mg/kg/day	26	SA, OL 19 months	NA	Controlled	Phe tolerance	-
<b>Registry data</b>						
PKUDOS	715	SA, OL 7 years	NA	Uncontrolled / Controlled	Phe tolerance Reduction blood Phe	-
KAMPER	575	SA, OL 7 years	NA	Uncontrolled / Controlled	Phe tolerance Reduction blood Phe	-

DB=double blind; OL=open label; pts = patients; R=randomised; SA = Single arm  
Source: Section 2 of the resubmission

6.10 PKU-003 and PKU-006 (Part 2) were considered to have a low risk of bias. SPARK, an open-label study, was considered to be at a moderate risk of bias. Although blood Phe levels are an objective outcome, knowledge of receiving treatment may influence a patient’s compliance with diet and consequently their blood Phe levels.

### **Comparative effectiveness**

6.11 The resubmission included a number of additional trials and studies compared with the previous submission. The data for the trials and studies previously considered remain unchanged from the November 2011 submission, however the totality of the evidence presented in the resubmission is provided below (shaded cells represent newly provided data).

6.12 Response rates to sapropterin were assessed in five studies, the results are presented in Table 7.

**Table 7: Response to sapropterin, defined as  $\geq 30\%$  reduction in blood Phe levels in studies PKU-001, EMR\_700773\_510, ENDURE, PKU-015 (Part 1), and defined as  $\geq 30\%$  reduction in blood Phe levels AND blood Phe  $\leq 300$   $\mu\text{mol/L}$  in PKU-006 (Part 1) - results for overall study populations and subgroup analysis by baseline characteristics are reported**

Study	Response		Patients
	n/N (%)	95% CI	
PKU-001, 10 mg/kg/day for 8 days	96/485 (20)	16, 23	$\geq 8$ years, baseline Phe $\geq 480$ $\mu\text{mol/L}$ , no strict diet
<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	
$\geq 1200$ $\mu\text{mol/L}$	13/136 (10)	NR	
EMR_700773_510, 20 mg/kg/day for 8 days	30/90 (33.3)	24, 44	4-18 years, baseline Phe $\geq 450$ $\mu\text{mol/L}$ , maintain diet
ENDURE, 20 mg/kg/day for 28 days	44/59 (75)	62, 85	$\geq 4$ years, baseline Phe $\geq 300$ $\mu\text{mol/L}$ , maintain diet
7 days	11/59 (64)	51, 77	
4-16 years	11/59 (64)	51, 77	
>16 years	11/59 (64)	51, 77	
$\leq 600$ $\mu\text{mol/L}$	11/59 (64)	NR	
600-1200 $\mu\text{mol/L}$	11/59 (64)	NR	
$\geq 1200$ $\mu\text{mol/L}$	11/59 (64)	NR	
PKU-006 (Part 1), 20 mg/kg/day for 8 days	50/90 (56)	NR	4-12 years, baseline Phe $\leq 480$ $\mu\text{mol/L}$ , strict diet
PKU-015 (Part 1), 20 mg/kg/day for 28 days	63/95 (66.3)	NR	0-6 years, baseline Phe not reported, strict diet

Source: Table 2-12, p74; Figure 2-4, p75; Table 2-15, p77; Table 2-17, p78; Table 20, p81; pp79-80 of the resubmission and Table 11.3, p58 of the PKU-001 CSR; Table 11-12, pp57-59 of the ENDURE CSR.

6.13 The response to sapropterin ranged from 20% (PKU-001) to 75% (ENDURE) for the whole study populations across the included studies. Response to sapropterin appeared to vary depending on:

- Sapropterin dose (20 mg/kg/day being better than 10 mg/kg/day);
- Test period duration (better response with a longer duration);
- Baseline Phe levels (better response with lower levels);
- Age (the PBAC noted there was better response among younger patients); and
- Adherence to a strict diet (rather than no strict diet).

6.14 The applicability of the response rates in the studies to the likely Australian population was uncertain. The resubmission suggested that responsiveness testing would involve treatment with sapropterin 10 mg/kg/day for 7 days, and if inadequate blood Phe reductions are achieved, dose may be increased weekly to 20 mg/kg/day for up to 28 days in total, which was not conducted in any of the studies.

6.15 The rates may also be underestimated as a review of the patients' medical history in PKU-015 (Part 1) increased the response rate to 75%. This type of review and re-assessment of response may be relevant to the assessment of response to be eligible for sapropterin on the PBS.

6.16 Reduction in blood Phe levels was assessed in two randomised trials (PKU-003 and PKU-006 (Part 2)) and two single-arm studies (PKU-004 and PKU-008). The results from the randomised trials are presented in Table 8.

**Table 8: Results for the change in blood Phe levels reported in the PKU-003 and PKU-006 (Part 2) randomised trials**

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 = <b>-245 (-350, -141)</b>
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)
PKU-006 (Part 2)			
Baseline, mean $\mu\text{mol/L}$ (SD)	N=33; 275.7 (135.2)	N=12; [REDACTED]	-51.9 (-197, 93.3)
3 weeks, mean $\mu\text{mol/L}$ (SD)	N=33; 127.2 (89.6)	N=12; [REDACTED]	
Change, mean $\mu\text{mol/L}$ (SD) – week 3 from baseline	N=33; -148.5 (134.2) <b>P&lt;0.001</b>	N=12; -96.6 (243.6) P=0.20	

Source: Table 2-35, p113; Tables 2-37 and 2-38, p115; Table 2-65, p167 of the resubmission and Table B.6.3, 5.7 COM.45, commentary on the November 2011 Sapropterin submission

6.17 A statistically significant reduction in blood Phe levels were observed among those treated with sapropterin 10 mg/kg/day compared with placebo, both in combination with a patient’s usual diet (abandoned strict low Phe diet) over 6 weeks in PKU-003. Additionally, a significantly greater proportion of sapropterin treated patients achieved blood Phe levels <600 and <360  $\mu\text{mol/L}$ . Notably however, the mean blood Phe levels among those treated with sapropterin was 607  $\mu\text{mol/L}$  following 6 weeks of treatment, with only 32% of patients achieving blood Phe levels  $\leq 360$   $\mu\text{mol/L}$  (the level recommended in guidelines).

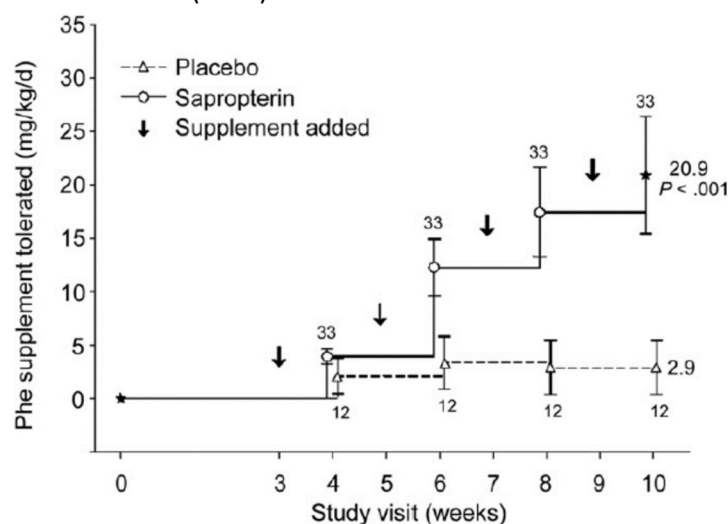
6.18 In Trial PKU-006 (Part 2) a statistically significant reduction in blood Phe levels was observed among those treated with sapropterin 20 mg/kg/day in combination with a strict diet for 3 weeks, while no statistically significant differences were observed in Phe blood levels between weeks 0 and 3 in those treated with placebo in combination with a strict diet. Although not reported in the resubmission (or the clinical study report for PKU-006 provided with the resubmission), there were no statistically significant differences in blood Phe levels in those treated with sapropterin + a strict diet versus a strict diet alone after 3 weeks of treatment.

6.19 Patients enrolled in PKU-004 were those who had completed PKU-003. A reduction in blood Phe was observed at all time points with treatment with sapropterin, with larger reductions observed with increasing doses of sapropterin, which were statistically significant.

6.20 Patients enrolled in PKU-008 are those who completed PKU-004 and -006 (Part 2). Overall, the mean blood Phe remained constant in both cohorts over 24 months.

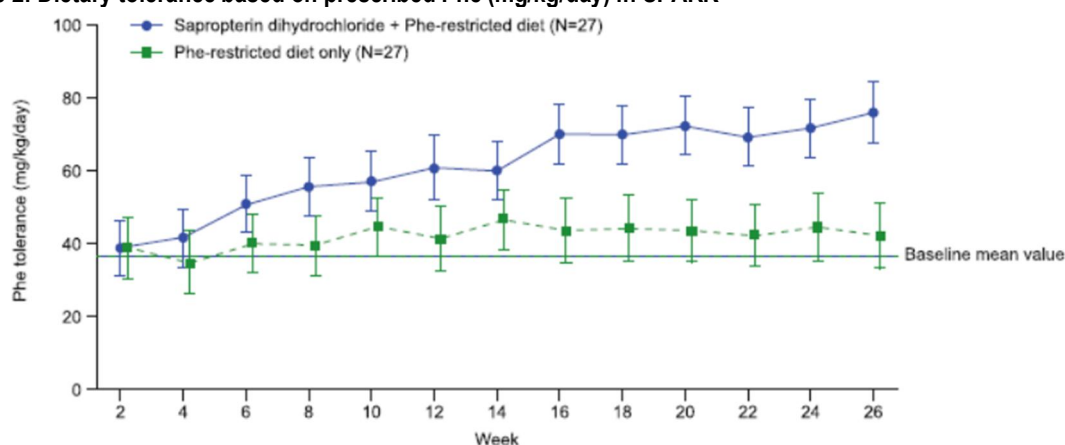
6.21 Changes in dietary Phe restrictions were reported in two randomised trials (PKU-006 (Part 2), SPARK) and two single arm studies (PKU-015 (Part 2), KOGNITO). The results from the trials are presented in Figures 1 and 2.

Figure 1: Total Phe supplement tolerated by patients receiving sapropterin 20 mg/kg/day or placebo, based on prescribed Phe supplements in PKU-006 (Part 2)



Source: Figure 2-11, p163 of the resubmission

Figure 2: Dietary tolerance based on prescribed Phe (mg/kg/day) in SPARK



Source: Figure 2-14, p170 of the resubmission

6.22 In PKU-006 (Part 2), over the 10-week period of the trial (Phe supplementation beginning from week 3), patients in the sapropterin group tolerated a mean  $\pm$  SD of  $20.9 \pm 15.4$  mg/kg/day of Phe supplementation which was a statistically significant increase from week 0 ( $P < 0.001$ ). Patients treated with sapropterin tolerated  $17.7$  mg/kg (95% CI: 9, 27 mg/kg) more Phe supplement than patients on placebo.

6.23 While the data suggest that in some patients initially well controlled on Phe-restricted diets, the addition of sapropterin may increase tolerance of dietary Phe while maintaining blood Phe at  $\leq 360 \mu\text{mol/L}$ , this is based on follow-up as short as 2 weeks. There are no data from this trial indicating whether treatment with

sapropterin allows meaningful changes in dietary restrictions for some patients over the long term. The ESC considered that this lack of data was a key issue because a substantial utility increase was associated with diet relaxation in the modelled economic evaluation.

- 6.24 A significant increase in prescribed dietary Phe over time in the sapropterin plus Phe-restricted diet group from a mean of 37.1 mg/kg/day to 80.6 mg/kg/day was observed in SPARK. In the Phe-restricted diet group only, there was a slight increase in dietary Phe from 35.8 mg/kg/day to 50.1 mg/kg/day. This difference was statistically significant, mean difference (95% CI) of 30.5 (18.7, 42.3) mg/kg/day and occurred while maintaining blood Phe levels between 120 and 360 µmol/L. Like PKU-006 (Part 2), this is based on tolerance periods as short as 2 weeks.
- 6.25 PKU-015 (Part 2) reported that despite the increases in dietary Phe, mean blood Phe levels remained within the recommended range for the 2-year duration of the analysis period (<360 µmol/L, with a goal of maintaining blood Phe levels between 120 to 240 µmol/L) and KOGNITO reported increasing Phe tolerance among those previously naïve to sapropterin increased over the study period, while Phe tolerance remained constant among continuing users over the 18 month period. Data from PKU-015 (Part 2) and KOGNITO indicate that treatment with sapropterin leads to an increased Phe tolerance over a period of up to two years. However, neither of these studies included a comparator group, thus the Phe tolerance levels among those not treated with sapropterin is unknown. Similar reports of continued Phe tolerance was reported in PKUDOS and KAMPER.

### ***Comparative harms***

- 6.26 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.
- 6.27 The most common events reported among the trials and studies were cough, upper respiratory tract infections and nasopharyngitis.

### ***Benefits/harms***

- 6.28 A summary of the comparative benefits for sapropterin + diet versus diet alone is presented in Table 9. No differences were observed for harms.

**Table 9: Summary of comparative benefits for sapropterin + diet versus diet alone**

<b>Continuous outcome I: change from baseline blood Phe levels</b>							
	<b>Sapropterin 10 or 20 mg/kg/day<sup>a</sup> + diet<sup>b</sup></b>			<b>Diet alone</b>			<b>Mean difference*: (95% CI)</b>
	<b>N</b>	<b>Mean Δ baseline blood Phe</b>	<b>SD</b>	<b>N</b>	<b>Mean Δ baseline blood Phe</b>	<b>SD</b>	
PKU-003	41	-239 μmol/L	SE: 38.3	47	6 μmol/L	SE: 35.8	<b>-245 (-350, -141)</b>
PKU-006 (Part 2)	33	-148.5 μmol/L	134.2	12	-96.6 μmol/L	243.6	-51.9 (-197, 93.3)
<b>Proportion of patients achieving blood Phe levels &lt;360 μmol/L (the target recommended in guidelines)</b>							
	Sapropterin 10 mg/kg/day <sup>b</sup>			Diet alone			
PKU-003	13/41 (32%)			1/47 (2%)			<b>RR = 14.9 (2.0, 109.1) RD = 0.3 (0.2, 0.4)</b>
<b>Continuous outcome II: change in Phe tolerance</b>							
	<b>Sapropterin 10 or 20 mg/kg/day<sup>a</sup> + diet</b>			<b>Diet alone</b>			<b>Mean difference*: (95% CI)</b>
	<b>N</b>	<b>Mean Δ baseline Phe tolerance</b>	<b>SD</b>	<b>N</b>	<b>Mean Δ baseline Phe tolerance</b>	<b>SD</b>	
PKU-006 (Part 2)	33	20.9mg	15.4	12	3.3	3.9	<b>17.7 (9, 27)</b>
SPARK	27	■ mg	NR	27	■ mg	NR	<b>30.5 (18.7, 42.3)</b>

<sup>a</sup> 10 mg/kg/day in PKU-003, 20 mg/kg/day in PKU-006 (Part 2); only 2 patients on 20 mg/kg/day in SPARK with remainder on 10 mg/kg/day

<sup>b</sup> not a strict diet in PKU-003, strict diet in PKU-006 (Part 2) and SPARK

Source: compiled during the evaluation

6.29 On the basis of direct evidence presented by the resubmission, the comparison of sapropterin + diet and diet alone resulted in:

- Approximately a 245 μmol/L reduction in blood Phe levels over a 6 week duration among patients not adhering to a strict diet;
- No difference in blood Phe levels over a 3 week duration among patients adhering to a strict diet; and
- Approximately a 17.7 mg increase in Phe tolerance over a 6 week duration among patients who were adhering to a strict diet; and
- Approximately a 30.5 mg increase in Phe tolerance over a 26 week duration among patients who were adhering to a strict diet.

6.30 After six weeks of therapy, only 32% of patients in PKU-003 (i.e. patients not adhering to a strict diet) achieved blood Phe levels ≤360 μmol/L (the level recommended in guidelines).

6.31 The resubmission attempted to inform what these reductions in blood Phe levels or increases in Phe tolerance would mean for a particular patient, by providing some evidence that IQ and neurocognitive effects are affected by increasing blood Phe levels and stating that it would enable some PKU patients to relax their restrictive Phe diet.

## **Clinical claim**

### Poorly-controlled Phe blood level sub-population

- 6.32 The resubmission described sapropterin plus a relaxed (“non strict”) diet compared with a relaxed diet alone as superior in terms of efficacy, based on the outcome of blood Phe levels. The resubmission claimed that sapropterin has non-inferior safety compared with a relaxed diet alone.
- 6.33 The PBAC considered that the resubmission’s claim of superior comparative effectiveness of sapropterin plus a relaxed diet versus a relaxed diet alone was adequately supported by the evidence presented. The PBAC noted that the randomised trial (PKU-003) demonstrated a statistically significant decrease in blood Phe levels among those treated with sapropterin plus a non strict Phe-restricted diet compared with those on a non strict Phe-restricted diet alone over 6 weeks.
- 6.34 However, the PBAC considered that the clinical significance of these benefits was not clearly described in the resubmission, noting that the mean blood Phe level was 607 µmol/L after 6 weeks of sapropterin treatment, with only 32% of patients achieving blood Phe levels ≤360 µmol/L (the level recommended in guidelines). Long-term data of continued use of sapropterin for up to six years also demonstrated continued decreased blood Phe levels, although approximately █% of those patients also failed to achieve target levels.
- 6.35 Although the resubmission presented data demonstrating a correlation between increased blood Phe levels and IQ and neurocognitive effects, the ESC considered that it was not clear how the observed changes in blood Phe levels would translate for a given patient. The ESC considered that, while sapropterin may improve blood Phe levels in some patients, the clinical impact of the likely changes in Australian practice was not clear (e.g. whether neurocognitive function would be improved compared with standard dietary management).

### Well-controlled Phe blood level sub-population

- 6.36 The resubmission described sapropterin as superior in terms of increasing Phe tolerance compared with a strict Phe-restricted diet alone. The resubmission claimed there would be no benefits in terms of blood Phe control in the well-controlled population given their blood Phe levels are already within the therapeutic range. The resubmission claimed that sapropterin has non-inferior safety compared with a Phe-restricted diet alone.
- 6.37 The PBAC considered that the resubmission’s claim that sapropterin has superior effectiveness, in terms of increasing Phe tolerance, compared with a strict Phe-restricted diet alone was adequately supported by the evidence presented. The PBAC noted that the randomised trials (PKU-006 (Part 2), SPARK) demonstrated a statistically significant increase in Phe tolerance among those treated with sapropterin compared with those on a strict Phe-restricted diet alone over 6 or 26 weeks. Long-term data of continued use of sapropterin for up to six years also

demonstrated continued increased Phe tolerance, although the contribution of increasing age and weight of the patients over time may have contributed to that observation.

- 6.38 The resubmission did not quantify the level of reduction in dietary Phe restriction that would result in a meaningful benefit for patients. The ESC considered that, while sapropterin may increase Phe tolerance in some patients, the resubmission did not outline the extent to which a patient's diet could be relaxed, and what impact this would have on patient outcomes or quality of life.
- 6.39 The pre-PBAC response stated that the results of PKU-006 (Part 2), as outlined in Paragraph 6.22, showed that patients aged 4-12 years on sapropterin tolerated 17.7 mg/kg (95% CI: 9, 27) more Phe supplement than patients on placebo. At baseline, these patients had Phe tolerance of approximately 17 mg/kg, hence sapropterin resulted in a doubling of Phe tolerance. The pre-PBAC response outlined that this may enable a 4 year old (weighing 15 kg) to consume an additional 5 g of protein, which corresponds with a slice of regular bread (3 g protein) and one banana (2 g). As a patient grows the amount of protein per day would also increase.

#### Both sub-populations

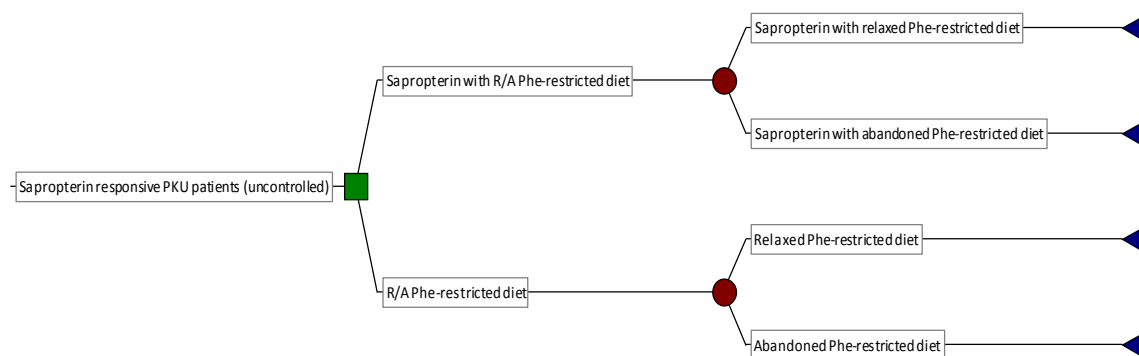
- 6.40 The ESC considered that the incremental health benefit of sapropterin over standard dietary management (either a relaxed or strict diet) in current Australian practice was unclear, particularly in terms of clinically meaningful health outcomes.
- 6.41 The PBAC considered that the potential benefits of sapropterin over dietary management alone in terms of meaningful patient-relevant outcomes, were not clearly demonstrated in the resubmission, but were identified by patients and their families in the consumer comments, clinician correspondence and at the consumer hearing.
- 6.42 The PBAC considered that the claim of superior comparative effectiveness versus either a relaxed or strict Phe-restricted diet was reasonable. The PBAC noted that that response to sapropterin appeared to vary across the studies, depending on a range of factors, including that there was better response among younger patients.
- 6.43 The PBAC considered that the claim of non-inferior comparative safety was reasonable for both sub-populations.

#### ***Economic analysis***

- 6.44 A modelled cost-utility decision-tree analysis was used, with separate analyses for cohorts by age with one ratio for adults. The clinical study data outlined above (in 'Clinical trials' and 'Comparative effectiveness') were not used to inform the model. Instead, the model was informed by epidemiological data that was not applicable to the Australian population (e.g. the studies were conducted in the US or UK, and from different time periods with one having been conducted in the 1970s, as outlined in Table 11).

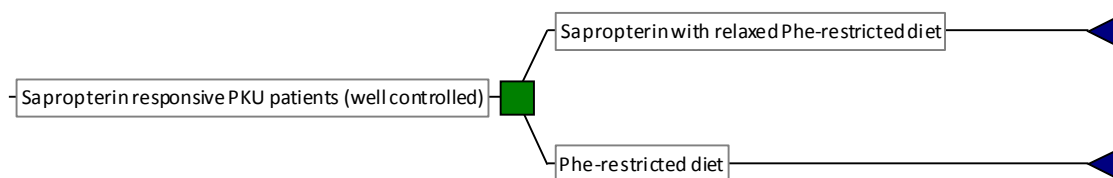
- 6.45 Two decision-tree analytic models with slightly different structures were used: one for the ‘poorly-controlled Phe level’ group; and one for the ‘well-controlled Phe level’ group, as shown in Figures 3 and 4, respectively. These were combined in a weighted analysis for the base-case economic evaluation.
- 6.46 Separate incremental cost-effectiveness ratios (ICERs) were calculated for each age between 0 and 17 years, and one for  $\geq 18$  years of age, rather than one lifetime ICER. This was based on feedback from the ESC from the previous submission.

**Figure 3: Decision-tree structure for the poorly-controlled sub-population analysis**



Source: Figure 3-8, p231 of the resubmission  
R/A = relaxed or abandoned

**Figure 4: Decision-tree structure for the well-controlled sub-population analysis**



Source: Figure 3-9, p231 of the resubmission

- 6.47 The ESC and the PBAC considered that basing the model on two discrete patient sub-groups was not reasonable as patients would likely cycle between the poorly-controlled and well-controlled groups over time.
- 6.48 Table 10 summarises the model structure and rationale. The economic evaluation differed to that presented in the November 2011 submission, which used a Markov model with a lifetime time-horizon for an <18 year-old population only.

**Table 10: Summary of model structure and rationale**

Component	Summary		
Time horizon	1 year (analyses conducted for each age from 0 -17 years old, and for an ≥18 group)		
Outcomes	Outcome of reduction in blood Phe-levels incorporated through the difference in utility values between relevant sapropterin and comparator health states. Outcome of reduction in Phe-free dietary restrictions incorporated through reduction in quantity of Phe-free supplement intake.		
Methods used to generate results	For each cohort, two decision-tree analytic models (one for the 'well-controlled Phe level' group and one for the 'poorly-controlled Phe level' group) were combined in a weighted analysis to formulate the base-case economic evaluation.		
Health states	In patients with poorly-controlled Phe levels: <ol style="list-style-type: none"> <li>1. Sapropterin + relaxed Phe-restricted diet</li> <li>2. Sapropterin + abandoned Phe-restricted diet</li> <li>3. Relaxed Phe-restricted diet</li> <li>4. Abandoned Phe-restricted diet</li> </ol> In patients with well-controlled Phe levels: <ol style="list-style-type: none"> <li>1. Sapropterin + relaxed Phe-restricted diet</li> <li>2. Phe-restricted diet</li> </ol>		
Utility values	Health state	Utility	Source
	Sapropterin + relaxed or abandoned diet	■	UK general public parent valuations of 'severe PKU controlled by drug' child health state using EQ-5D
	Strict Phe-restricted diet	■	unclear
	Relaxed Phe-restricted diet	■	unclear
	Abandoned Phe-restricted diet (i.e. uncontrolled PKU)	■	UK general public parent valuations of 'uncontrolled PKU' child health state using EQ-5D

Source: Section 3 of the resubmission

<sup>a</sup> The ESC noted that as a straight linear relationship was assumed between ■ and ■, then the utility value should be ■ (rather than ■) as outlined on pages 79 to 80 of the commentary (7.05.COM.79-80).

### Utilities

6.49 The ESC considered that the utility weights (outlined in Table 10) applied in the model lacked face validity because:

- applying a utility of ■ to all patients receiving sapropterin, regardless of whether the benefit was reduced blood Phe (in the poorly-controlled group) or increased Phe tolerance (in the well-controlled group) was not reasonable. In the poorly controlled group, the utility of ■ was applied regardless of actual change in blood Phe levels, despite only 32% of patients achieving blood Phe levels ≤ 360 µmol/L (the target range) in Trial PKU-003. In the well-controlled group, there was no evidence to support the extent of relaxation of diet that would be achieved in clinical practice;
- the use of the same utilities for both adults and children was not clinically plausible. For example, the utility value of ■ (for the 'abandoned Phe-restricted diet, i.e. uncontrolled PKU, health state) was based explicitly on a child health-state. The PBAC considered that it is highly likely that potential health impacts of uncontrolled PKU are more severe in infants and young children than in adults;
- the utility weight for the 'abandoned Phe-restricted diet' health state included behavioural impacts and the impact on parents, which were not appropriate for inclusion in the base case (refer to Section 3A.5, page 76, Guidelines for preparing

- a submission to the PBAC, Version 5.0, September 2016);
  - when compared with weights for other conditions with potentially similar behavioural and functional impacts (such as attention deficit hyperactivity disorder [ADHD]), the weights used in the economic evaluation appeared implausible. The pre-PBAC response stated that while some aspects of PKU resemble ADHD, the quality of life impacts of PKU extend beyond those of ADHD; and
  - the resubmission assumed that the disutility associated with adhering to a Phe-restricted diet (■■■■ – ■■■■ = ■■■■) would be the same as the disutility associated with uncontrolled PKU (i.e. the abandoned Phe-restricted diet; ■■■■ – ■■■■ = ■■■■) despite uncontrolled PKU in children potentially leading to irreversible neurological, behavioural and physiological sequelae.
- 6.50 The PSCR acknowledged the limitations of the utility values but argued that no alternatives were available. Overall, the ESC and the PBAC considered that the utility values, which were key drivers of the model, were implausible.

Proportion of patients in the poorly-controlled verses well-controlled Phe level groups

- 6.51 The proportion of patients in the ‘well-controlled Phe level’ group was assumed to be 82% for ages 0 to 12, 85% for ages 13 to 17, and 33% for ages ≥ 18 years. This was based on an epidemiological study, Freehauf 2013, which used blood-level data from a US database. The data were from 76 patients aged ≤ 21 years who received dietary management from 2000 to 2005. Median Phe-levels were calculated over five years and the proportion of patients in each age group (0-12 years, 13-17 years and ≥18 years) who had median Phe levels within the target range were calculated.
- 6.52 A number of issues were identified with applying data from Freehauf 2013 in the economic model:
- patient numbers in the 13-17 and ≥ 18 year age groups were low (13 and 12 patients, respectively) and the ≥ 18 year age group comprised young adults only; and
  - the ESC and the PBAC considered that Freehauf 2013 was unlikely to be applicable to the PBS population. For example the study was conducted in the US where dietary management and access to supplements may differ from current Australian clinical practice. Further, patient characteristics were not available (such as Phe blood levels at diagnosis).
- 6.53 Table 11 summarises the key model drivers.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact/Direction of bias
Proportion of 'well-controlled' vs 'poorly-controlled' Phe blood level patients	Epidemiological estimates by age taken from the literature (Freehauf et al 2013).	High. 'Poorly-controlled' sub-group has substantially lower ICERs, thus these epidemiological inputs are key cost drivers. Unclear direction of bias as the proportions in the PBS population are unknown.
Proportion on a 'relaxed' versus an 'abandoned' diet in the comparator arm (of the poorly-controlled group)	Epidemiological studies. Smith 1991 for ages 0 to 17, Koch 2002 for ≥ 18 years.	Moderate. Unclear direction of bias. Smith 1991 was UK study of patients born in 1972-1978. Koch 2002 was a US study based on 73 young adults, data were from the 1990s. The methodology and the applicability of both studies to the current Australian population were unclear (e.g. it was unclear if the dietary cut-offs are applicable and if adherence has changed since the time the studies were conducted).
Sapropterin health states utility value	Utility value (████) derived from YHEC Utility Study for the 'Child Severe PKU controlled by drug' health-state using the EQ-5D.	High. Unclear direction, but the assumption of the same utility being applied to those benefitting from blood Phe reductions and those benefitting from relaxation of diet while maintaining target levels appeared implausible.
'Strict Phe-restricted diet' health state utility value	Utility value (████) taken from November 2011 evaluator-conducted sensitivity analyses, the derivation of which is unclear.	High. Unclear direction as source of utility not reported. Results in a █████ utility increment being associated with relaxation of diet among those "well controlled", when these patients may not change diet and thus would benefit only from further blood Phe level reductions of unknown clinical significance.
'Abandoned Phe-restricted diet' (i.e. uncontrolled PKU) health state utility value	Utility value (████) derived from YHEC Utility Study 'uncontrolled PKU child health states.	High. Favours sapropterin. Such a low utility value appeared implausible given the likely impacts within an Australian population of children (the resubmission did not present evidence showing the prevalence of detrimental health outcomes in the current Australian population). Implausible value for adults.

Source: Section 3 of the resubmission

YHEC = York Health Economics Consortium

<sup>a</sup> The ESC noted that as a straight linear relationship was assumed between █████ and █████, then the utility value should be █████ (rather than █████) as outlined on pages 79 to 80 of the commentary (7.05.COM.79-80). Thus the increment between the "sapropterin" health state and the "strict Phe-restricted diet" health state would be █████

6.54 Table 12 summarises the results of the economic evaluation. The two decision-tree analytic models (for the poorly-controlled and the well-controlled Phe-level groups) were combined in a weighted analysis to estimate the base-case ICER for each age.

Table 12: Results of the economic evaluation – weighted analysis of the poorly- and well-controlled groups

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

Source: Tables 3-20 and 3-21 pp256-7 of the resubmission; Table 3-10 of the resubmission

The redacted table shows ICERs in the range of less than \$15,000/QALY – more than \$200,000/QALY.

- 6.55 Treatment with sapropterin was estimated to be more cost-effective among the ‘poorly-controlled’ sub-population. This highlights that splitting the population into the two sub-populations is a key issue, particularly given the lack of reliable data and clinical rationale to inform the proportional-split. The key driver of the difference between the two sub-populations were the lower quality-adjusted life years (QALYs) accrued in the ‘poorly-controlled’ comparator arm (utility value between [redacted] and [redacted], depending on age) compared with the ‘well-controlled’ comparator arm (utility of [redacted]), while the drug cost of sapropterin was the same in the two sub-populations.
- 6.56 These results indicate that the gain in health benefit in patients taking sapropterin to reduce blood Phe-levels is substantially greater than the gain in health benefit in patients taking sapropterin to reduce dietary restrictions, particularly in adults.
- 6.57 Overall, the ESC considered that the model lacked face validity and considered that it was implausible that the same incremental outcomes were derived for all patients in the well controlled Phe group (utility gain of [redacted] each year) and for all patients aged 2 to 17 years in the poorly controlled group (utility gain of [redacted] each year).
- 6.58 The ICER generally increased with age because the dose of sapropterin is weight-based (although the ICER decreased after 17 years of age because the proportion of patients assumed to be poorly controlled increased from 15% to 67%). The ESC noted that the majority of people with PKU would be adults, so the ICER in patients

aged  $\geq 18$  years, more than \$200,000/QALY, would more closely reflect the overall cost-effectiveness of sapropterin in the Australian population.

- 6.59 The PBAC considered that the economic model may not have accurately captured the additional benefits of sapropterin in children relative to adults. For example, the model used the same utilities for adults and children, despite the potential health impacts of uncontrolled PKU being irreversible and more severe in children compared with adults.
- 6.60 Univariate sensitivity analyses were presented in the resubmission, which showed the proportion of individuals with well- versus poorly-controlled blood Phe levels was a key driver of the economic model. The ESC considered that the sensitivity analyses were not informative given the significant issues identified with the model utilities and the differentiation of the population into poorly-controlled and well-controlled sub-groups.
- 6.61 The ICERs estimated in the November 2011 submission were more than \$200,000/QALY (versus strict diet), \$105,000/QALY - \$200,000/QALY (versus relaxed diet) and \$75,000/QALY - \$105,000/QALY (versus uncontrolled diet). The November 2011 submission reported a base case ICER of \$105,000/QALY - \$200,000/QALY (the submission used the relaxed diet as the comparator in the base case as this was considered to be reflective of 'real life' compliance with diet restrictions and supplements).

### ***Drug cost/patient/year***

- 6.62 The cost of sapropterin per patient per year ranged from \$ [REDACTED] in the 0-year old cohort to \$ [REDACTED] in the  $\geq 18$  year-old cohort. These costs were determined by applying the proposed effective sapropterin DPMQ (\$ [REDACTED]) to mean weight-by-age data and a mean daily dose of [REDACTED] mg/kg/day (derived from trial/study evidence, although this may have been underestimated).

### ***Estimated PBS usage & financial implications***

- 6.63 The resubmission was considered by DUSC. An epidemiological approach was used. The key sources used were Boneh et al (2006) and Abadie et al (2001) for estimates of PKU prevalence requiring treatment for HPA in the population, clinical trial evidence for estimates of the proportion of PKU sapropterin-responders and inputs used to inform the economic analysis.
- 6.64 The financial estimates largely depended on the assumed sapropterin response rates. DUSC noted that a patient's response to sapropterin appeared to be influenced by a range of factors including dose, test period duration, baseline Phe levels, age and adherence to a strict Phe-restricted diet. DUSC considered that the method for determining sapropterin response rates, particularly the role of clinical judgement regarding the extent of illness and dietary adherence, generated uncertainty in the financial estimates. DUSC also considered that there was

ambiguity in what constituted a response, and reiterated its concerns that the restriction is likely to allow use of sapropterin in a broader population than the eligible population used in the estimates.

- 6.65 Response was assumed to vary for people with “well-controlled” versus “poorly-controlled” blood Phe levels. The resubmission estimated that 82% of 0-12 year olds, 85% of 13-17 year olds and 33% of those aged  $\geq 18$  years were “well” controlled, with the remainder being “poorly” controlled; based on Freehauf et al (2013). The DUSC considered that these estimates might not be applicable to the likely PBS population as: it was unclear how patients that crossed age boundaries were categorised in the study; the sample sizes were small for those aged 13-17 years and for adults; and the adult population in the study only included those aged 18-26 years.
- 6.66 The resubmission subsequently applied the derived Day 28 sapropterin response rates (■% for well-controlled and ■% for poorly controlled) to each age group to estimate the proportion of responders. The DUSC considered that the applicability of these response rates was uncertain, given none of the studies included the responsiveness regimen suggested by the resubmission, the studies reporting response rates for those “well” controlled only included patients aged  $< 12$  years and baseline blood Phe levels among those “poorly” controlled in the PBS population are unknown, and response rates in the studies appeared to be better with an increased sapropterin dose, increased test period duration, lower baseline Phe levels and decreasing age.
- 6.67 DUSC considered that the estimates presented in the resubmission were underestimated. The DUSC considered that the main issues were:
- The financial estimates largely depend on the assumed sapropterin response rates. Response to sapropterin appears to be influenced by a number of factors and there is a high degree of clinical subjectivity in determining a response.
  - The proportion of sapropterin responders and the estimated sapropterin uptake rates may not be applicable to the PBS population.
  - The exclusion of patients over the age of 51 in determining the eligible population was inappropriate, given age criteria were not specified in the requested restriction. This potentially excluded some eligible patients.
  - The clinical algorithm recommended treatment at blood Phe levels  $\geq 360$   $\mu\text{mol/L}$  whereas the eligible population was determined using a threshold of  $> 300$   $\mu\text{mol/L}$ . This overestimates the eligible population.
  - The uptake rates are likely underestimated given that no other alternative treatments are available other than the Phe-restricted diet; sapropterin appears to be well tolerated; and there are severe health impacts for the patient if the condition is not well-managed.
  - The estimated annual number of prescriptions may be over or underestimated due to inappropriate rounding of the average dosage amount. The direction of the uncertainty varies by patient age group.

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- A 100% compliance rate may not appropriately reflect a real world situation.
- The use of a single proxy for all Phe-free protein supplements was not appropriate; the cost offsets are therefore uncertain and might not be realised.

6.68 Table 13 summarises the estimated use and financial implications.

**Table 13: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated						
Number of scripts dispensed <sup>a</sup>						
<b>Estimated financial implications of sapropterin</b>						
Cost to PBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Cost to PBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for Phe-free amino acid supplements</b>						
Cost to PBS <sup>b</sup>	-\$	-\$	-\$	-\$	-\$	-\$
Co-payments <sup>b</sup>	\$	\$	\$	\$	\$	\$
Cost to PBS less co-payments <sup>b</sup>	-\$	-\$	-\$	-\$	-\$	-\$
<b>Net financial implications</b>						
Net cost to PBS	\$	\$	\$	\$	\$	\$

Source: Commentary Table 12, p19;

PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme

<sup>a</sup> Assuming 12.18 scripts per year as estimated by the submission.

<sup>b</sup> Estimates consistent with submission but as raised in the PSCR were noted incorrectly in the Commentary Table 12, p19.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000.

6.69 The resubmission estimated that the net cost to the PBS/RPBS would be \$20 - \$30 million in Year 6 and more than \$100 million over the first six years of listing.

### Quality Use of Medicines

6.70 DUSC was concerned that sapropterin use may allow inappropriate relaxation of the Phe-restricted diet. DUSC noted the importance of the Phe-restricted diet in the current treatment algorithm for the management of PKU and considered that there are substantial risks associated with non-adherence to a Phe-restricted diet.

### Financial Management – Risk Sharing Arrangements

6.71 The resubmission did not request a risk sharing arrangement (RSA). However, the pre-PBAC response proposed an RSA whereby Commonwealth expenditure would be capped at the estimates provided in Table 13 (based on the “Cost to PBS less co-payments” row) with a % rebate for all Commonwealth expenditure above this level.

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

## 7 PBAC Outcome

7.1 The PBAC deferred its decision about whether to recommend listing sapropterin for the treatment of patients with hyperphenylalaninaemia (HPA) caused by

phenylketonuria (PKU). The PBAC sought further evidence regarding processes for determining whether or not a patient is responsive to sapropterin and the patient population in which treatment would result in the greatest benefit, in terms of clinically significant outcomes such as cognitive function and supporting growth. The PBAC considered the greatest benefits would be experienced in children and adolescents, and sought further advice regarding the age level of patients who would benefit most from sapropterin therapy.

- 7.2 The PBAC noted this is a small patient population, and considered there were equity of access issues given that hospital-funded access was available in some states but not others. In deciding to defer, the PBAC acknowledged the input received from individuals, organisations and health professionals.
- 7.3 The PBAC 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. The PBAC also noted that the further benefits of sapropterin therapy described by patients and their families, which included a reduced risk of diabetes, reduced weight gain, improved growth and social inclusion. The PBAC considered that the consumer input had helped define the incremental benefits of sapropterin over dietary management, in terms of meaningful patient-relevant outcomes, particularly in children and adolescents.
- 7.4 As such, the PBAC considered that commencement of sapropterin therapy should be restricted to children and adolescents. The PBAC acknowledged that consumers had described a range of important benefits associated with lowering and stabilising Phe levels in adults, particularly during pre-conception and pregnancy, but considered that the resubmission had not provided sufficient evidence to support PBS-listing in these groups.
- 7.5 The PBAC considered that the patient representatives and community correspondence indicated that patients had realistic expectations about the likely outcomes of sapropterin treatment, including that not all patients would respond and that responsive patients would still need to adhere to a strict diet (although more liberal than without sapropterin).
- 7.6 The PBAC noted that the resubmission's proposed definition of initial response was achievement of either: a  $\geq 30\%$  reduction in blood Phe levels over a four-week period; or therapeutic blood Phe goals as defined for an individual patient by the treating physician. The PBAC considered that the latter criterion (i.e. Phe goals defined by the treating physician) should not be included in the initiation criteria as it is broad and subjective.
- 7.7 Further, the PBAC considered that insufficient evidence had been presented for the Committee to be confident that the sapropterin responsiveness test proposed by the resubmission would identify truly responsive patients in terms of correctly identifying patients who are and patients who are not responsive. In particular, the PBAC considered that it would be difficult to distinguish true responsiveness from

fluctuations in Phe levels due to other causes such as changes in diet or intercurrent illness, particularly given the high underlying variability in Phe levels and the long period of testing proposed (four weeks). The PBAC considered that further evidence was required regarding sapropterin responsiveness testing, and assessment of ongoing response.

- 7.8 The PBAC noted that the evaluation and DUSC had identified a number of other issues with the proposed restrictions, such as accessing sapropterin for the purpose of responsiveness testing, grandfathering requirements, auditing requirements and assessing continuing response (refer to Paragraphs 2.5 to 2.7). The PBAC considered that many of these issues hinged on the processes for assessing initial responsiveness and would also need to be addressed as part of the deferral process.
- 7.9 The PBAC considered that the resubmission's approach of splitting the patient population into those with poorly-controlled and those with well-controlled blood Phe levels (for the purpose of nominating differential comparators, outcomes and economic models) was not informative because these were not two distinct sub-populations.
- 7.10 The PBAC considered that the claim of superior comparative effectiveness versus either a relaxed or strict Phe-restricted diet was reasonable.
- 7.11 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.12 The PBAC considered that the ICER was unreliable as it was based on:
- utility weights that lacked face validity. In particular, the PBAC considered that the use of the same utilities for both adults and children was not clinically plausible, as the potential health impacts of uncontrolled PKU are more severe in children;
  - weighting the ICER between two sub-groups (those with poorly-controlled and well-controlled Phe levels) which was not reasonable as patients would cycle between the two sub-groups over time; and
  - epidemiological data that were not applicable to the Australian population. For example, the PBAC noted that data informing the 18 years and over age group in the economic model was based on young adults only.
- 7.13 The PBAC considered that the resulting ICER for patients aged 18 years and over, of more than \$200,000/QALY, was unacceptably high. The PBAC noted the ICERs for patients under 18 years of age were generally lower (starting at \$45,000/QALY - \$75,000/QALY in patients aged zero). While the PBAC considered that the ICERs were high in children and adolescents, the Committee considered that the clinically significant outcomes in younger patients may not have been fully captured in the economic evaluation.
- 7.14 The PBAC considered that an RSA would be required to manage the high and

uncertain cost-effectiveness and the uncertain patient population. The PBAC considered that the RSA should include 100% rebates for expenditure beyond the cap.

- 7.15 The PBAC noted that the financial estimates largely depended on the proportion of patients identified as being responsive to sapropterin. The PBAC considered that these proportions may need to be updated based on further deliberations regarding the processes for initial responsiveness testing.
- 7.16 The PBAC also noted that the financial estimates were based on utilisation in patients up to 51 years of age, and considered these would need to be updated to reflect commencement in children and adolescents only. The PBAC also considered that: the eligible population may be overestimated due to inconsistencies between the clinical guidelines and the criteria used to determine the eligible population; the uptake and compliance rates were underestimated; and that the resubmission's rounding of doses was inappropriate (as outlined in Paragraph 6.68).
- 7.17 In deferring making its decision on whether to list sapropterin for the treatment of PKU, the PBAC considered the following issues would need to be addressed: further advice was required regarding the age level of patients who would benefit most from sapropterin therapy; further evidence was required regarding responsiveness testing; an updated ICER; and a revised RSA was required based on updated financial estimates.
- 7.18 The PBAC noted that this resubmission is not eligible for an Independent Review as it has been deferred.

**Outcome:**

Deferred

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

BioMarin would like to recognise the input received from patients, families and health professionals. BioMarin would also like to thank the PBAC for its consideration of PKU, a rare disease affecting about 1 in 15,000 newborns in Australia. BioMarin looks forward to continuing to work with the PBAC and Department of Health to improve access to innovative medicines for patients with PKU.