An addendum to this minute has been included at the end of the document.

7.12 SAPROPTERIN, Powder for oral solution 500 mg, Tablet (soluble) 100 mg, Kuvan®, BioMarin Pharmaceutical Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission requested a General Schedule, Authority Required listing in combination with a phenylalanine (Phe)-restricted diet for the treatment of maternal phenylketonuria (MPKU) where a Phe-restricted diet does not adequately reduce blood Phe levels.

1.2 The minor resubmission requested listing of sapropterin in MPKU patients who have not previously initiated treatment with sapropterin, are 18 years or older, and are pregnant or actively planning to become pregnant (Table 1).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Maternal phenylketonuria
Intervention	Sapropterin 5-20 mg/kg/day (in combination with a Phe-restricted diet)
Comparator	Phe-restricted diet
Outcomes	Blood Phe levels Dietary Phe intake
Clinical claim	In patients with MPKU, sapropterin in combination with a Phe-restricted diet is more effective than a Phe-restricted diet at reducing blood Phe levels and increasing dietary Phe intake

Source: Table 1-1 from the submission

2 Background

Registration status

2.1 Sapropterin was TGA registered on 21 October 2010 for "the treatment of hyperphenylalaninaemia (HPA) in sapropterin-responsive adult and paediatric patients with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency".

Previous PBAC consideration

2.2 The PBAC had not previously considered a submission specifically for the treatment of HPA due to MPKU.

2.3 Sapropterin was previously considered by the PBAC for HPA due to PKU. A summary of the relevant prior PBAC considerations is provided below.

Table 2: Previous PBAC considerations

Meeting date	Request	Outcome	Detail
March 2018	The submission requested PBS-listing for the treatment of all sapropterin responsive patients, irrespective of age or Phe blood levels.	Deferred	The PBAC deferred its decision to recommend sapropterin for HPA due to PKU to seek 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 (Para 7.1, sapropterin PSD, March 2018 PBAC Meeting).
November 2018	The minor resubmission requested PBS-listing for the treatment of all sapropterin responsive patients. The basis for the requested listing remained unchanged and was a cost-utility analysis compared with a strict / relaxed / abandoned Phe-restricted diet and Phe-free supplements.	Recommended	The PBAC recommended extending the PBS-listing of sapropterin to include the treatment of HPA due to PKU in patients who are under 18 years of age. The PBAC was satisfied that sapropterin provides, for some patients, a significant improvement in efficacy over a Phe-restricted diet alone. In making this recommendation, the PBAC noted there was a high clinical need in a small patient population. The PBAC considered that an RSA would be required to manage the high and uncertain cost-effectiveness, the uncertain patient population, and the risk of use in patients not continuing to respond (Para 6.1, sapropterin PSD, November 2018 PBAC Meeting).

Source: Compiled during preparation of the Minor Overview
PSD = public summary document

2.4 As part of the March 2018 consideration, representatives of the PBAC met with representatives of the Metabolic Dietary Disorders Association (MDDA) prior to the PBAC meeting. 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 (paragraph 6.3, sapropterin public summary document (PSD), November 2018 PBAC Meeting). In March 2018, 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 re-submission had not provided sufficient evidence to support PBS-listing in these groups (para 7.4, sapropterin PSD, November 2018 PBAC meeting).

2.5 The PBAC previously recommended sapropterin for the treatment of PKU, but only in patients younger than 18 years at the time of commencing sapropterin, as the PBAC considered that the greatest clinical benefits would be achieved in children and adolescents (para 6.2, sapropterin PSD, November 2018 PBAC meeting).

2.6 In March 2018, the PBAC considered that the economic model was unreliable as: the utility weights lacked face validity; weighting the ICER between two sub-groups (those with poorly-controlled and well-controlled Phe levels) was not reasonable as patients would cycle between the two sub-groups over time; and the model was based on epidemiological data that were not applicable to the Australian population (especially in patients aged ≥ 18 years) (para 7.12, sapropterin PSD, March 2018 PBAC meeting). These issues were more relevant to the cohort of patients aged ≥ 18 years. While these issues remained in the November 2018 submission, the PBAC "considered that the incremental cost-effectiveness ratio estimated in the resubmission was high, the Committee acknowledged the high clinical need in this small patient group and considered that the clinically significant outcomes in patients under the age of 18 may not have been fully captured in the economic evaluation" (para 6.10, sapropterin PSD, November 2018 PBAC meeting).

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

3 Requested listing

3.1 The minor resubmission sought to add the following new, separate listing to the existing listings (not shown below). Secretariat suggested additions are in italics and deletions are in strikethrough; these changes relate to formatting of the restriction only.

MEDICINAL PRODUCT medicinal product pack	Treatment phase	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SAPROPTERIN						
sapropterin dihydrochloride 100 mg soluble tablet, 30	Initial treatment – responsiveness testing	11676M	3	90	0	Kuvan
	First continuing treatment Subsequent continuing treatment	11691H	6	180	5	Kuvan
sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	Initial treatment – responsiveness testing	11971C	1	30	0	Kuvan
	First continuing treatment Subsequent continuing treatment	11983Q	1	30	5	Kuvan

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	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.*
	Condition: Hyperphenylalaninaemia (HPA) ~~due to phenylketonuria (PKU)~~
	Indication: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: Initial treatment – responsiveness testing
	Clinical criteria:

	Patient must be actively planning to become pregnant or pregnant
	AND
	Clinical criteria:
	Patient must have a baseline blood phenylalanine level above 250 ~~µmol~~/*micromole per* L
	AND
	Clinical criteria:
	The treatment must be for the purpose of initial responsiveness testing for a period of 7 days
	AND
	Treatment criteria:
	Must be treated by a metabolic physician
	AND
	Population criteria:
	Patient must be 18 years of age or older
	Prescribing Instructions: Dietary phenylalanine intake must be maintained at a constant level
	Prescribing Instruction: ~~**Administrative Advice:**~~ *A patient may qualify for PBS-subsidised treatment under this restriction once only.* ~~Patients 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.~~
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction Type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	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.*
	Condition: Hyperphenylalaninaemia (HPA) ~~due to phenylketonuria (PKU)~~
	Indication: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	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
	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
	AND
	Clinical criteria:
	Patient must be actively planning to become pregnant or pregnant
	AND
	Clinical criteria:
	Patient must be undergoing regular phenylalanine testing *and assessment of adherence to dietary modifications*
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must be undergoing regular assessment of adherence to dietary modifications~~
	AND
	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
	AND
	Population criteria:
	Patient must be 18 years of age or older
	Prescribing Instructions: Blood phenylalanine levels must be based on measurements taken during stable periods of the condition
	Prescribing Instructions: ~~Total treatment with sapropterin~~ *Treatment with this drug* will not exceed 22 months for each pregnancy ~~(includes time for planning and becoming pregnant) and treatment will be stopped after delivery of the baby~~
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction Type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	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.*
	Condition: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	Indication: Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: Subsequent continuing
	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 actively planning to become pregnant or pregnant
	AND
	Clinical criteria:
	Patient must be undergoing regular phenylalanine testing *and assessment of adherence to dietary modifications*
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must be undergoing regular assessment of adherence to dietary modifications~~
	AND
	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
	AND
	Population criteria:
	Patient must be 18 years of age or older
	Prescribing Instructions: Blood phenylalanine levels must be based on measurements taken during stable periods of the condition
	Prescribing Instructions: ~~Total treatment with sapropterin~~ *Treatment with this drug* will not exceed 22 months for each pregnancy. ~~(includes time for planning and becoming pregnant) and treatment will be stopped after delivery of the baby~~

3.2 The proposed initial treatment – responsiveness testing and first continuing treatment restrictions require that within 7 days the patient must have demonstrated a response to treatment with this drug of at least a 30% reduction in Phe levels from baseline.

This is consistent with the current PKU restriction. While a one month responsiveness testing period was outlined in the Product Information (PI), the PBAC previously considered that it would be difficult to distinguish true responsiveness from fluctuations in Phe levels over one month due to other causes such as changes in diet or intercurrent illness, particularly given the high underlying variability in Phe levels. The PBAC previously recommended a 7 day responsiveness testing period for patients aged one month to 17 years, noting that the Australian guidelines for 'BH4 in the Management of PKU' discuss testing over a 7 day period, incorporating a pre-test Phe load, in patients aged 2-18 years (paragraphs 2.6 to 2.10, sapropterin PSD, November 2018 PBAC Meeting). The PBAC considered that these shorter testing periods were necessary to provide greater certainty that patients accessing sapropterin are truly responsive, and would provide increased confidence around the incremental effectiveness that would be achieved in clinical practice (para 6.5, sapropterin PSD, November 2018 PBAC Meeting). For the newly proposed MPKU responsiveness test listing, the proposed maximum quantities need to cater for a patient of adult weight (the financial estimates assumed an average weight of 71 kg for a female aged 18 years or over) who is likely to be dosed at 10 mg/kg once daily (but potentially as high as 20 mg/kg once daily), for up to 7 days, and be mindful that two presentations are available (500 mg sachets and 100 mg tablets).

3.3 In clinical practice, initial responsiveness testing often involves a pre-test Phe load. Clinicians will likely be reluctant to perform responsiveness testing in women who are pregnant or actively trying to conceive due to the teratogenic effects of a Phe load during this period. The pre-PBAC response acknowledged that there are clinical recommendations to consider a pre-test Phe load when baseline blood Phe levels are low (120-240 µmol/L), to ensure that the response can be attributed to sapropterin, rather than to over-restriction of dietary Phe. The pre-PBAC response stated that guidelines recommend that patients consult with a metabolic MPKU multidisciplinary team at least 4 months prior to conception and that if the clinician wishes to add a pre-test Phe load, this could be done during this pre-conception period. However, the PBAC noted that guidelines recommend maintaining blood Phe in the range of 70-250 µmol/L in the 3 months prior to conception, and the PBAC also considered there may be a risk of unplanned pregnancies during the pre-conception period. The PBAC considered that load testing should optimally occur before the pre-conception period.

3.4 The minor submission requested a total maximum treatment duration of 22 months in the restriction, noting that this was the treatment period recommended in May 2016 by the Pharmacology and Therapeutics Advisory Committee (PTAC) for the listing of sapropterin for MPKU by PHARMAC in New Zealand (paragraph 11.26, May 2016 PTAC meeting minutes). The PTAC authority form[1] requires that a blood Phe below

[1] *Form SA1923* - APPLICATION FOR SUBSIDY BY SPECIAL AUTHORITY for sapropterin dihydrochloride, https://www.pharmac.govt.nz/2020/10/01/SA1923.pdf

250 µmol/L is achieved within 2-4 weeks. The 22 month period allows for 1 month to achieve regulated Phe levels, 12 months for conception and 9 months for the ante-natal period. However, the following issues may arise if the PBS listing is capped at 22 months treatment duration :

- The Australasian MPKU Guidelines recommend maintaining blood Phe in the range of 70-250 µmol/L in the 3 months prior to conception and for the duration of the pregnancy (Inwood et al., 2015). The evidence presented in the guidelines suggests that it can take up to 3 months to achieve a Phe below 250 µmol/L, but in practice it can take longer (up to 6 months) for a sapropterin naïve patient to achieve a stable blood Phe within the specified range.
- It may take longer than 12 months to conceive; if conception does take longer than 12 months, ceasing sapropterin suddenly during pregnancy could be harmful to the unborn child and the mother.
- Ceasing sapropterin treatment suddenly post-partum can result in fluctuation of blood Phe levels, and may have adverse mental health effects on new mothers due to the neurological effects of HPA. The minor resubmission did not provide any information on the safety of the post-partum treatment withdrawal.

3.5 The pre-PBAC response acknowledged that specific allowances may be required for longer durations of therapy in some patients (e.g. patients who experience fertility issues, or to allow use in the immediate post-partum period) and stated that the sponsor is amenable to an alternative treatment duration as guided by the PBAC and expert clinical opinion.

3.6 The PBAC noted that the proposed restriction stated a treatment period 'for each pregnancy'. The PBAC noted that this would appropriately allow a patient to access sapropterin multiple times for multiple pregnancies (and would allow for longer treatment in the event of miscarriage).

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

4 Population and disease

4.1 PKU, also known as phenylalanine hydroxylase (PAH) deficiency, is a rare inborn error of metabolism with an incidence of 1:11,226 in Australia (Boneh et al., 2006). PKU results in an accumulation of Phe in the blood and brain of affected individuals due to mutations in the PAH gene, which results in defective PAH enzymes unable to effectively convert the amino acid Phe to tyrosine. If left untreated, it can cause severe neurocognitive delay and mental retardation, neuromotor disability, and adverse pregnancy outcomes for affected women. Current treatment of HPA in PKU is with a strict, lifelong low Phe diet achieved by controlled dietary restriction of whole protein, with concomitant administration of commercial Phe-free protein supplements (section 5, sapropterin PSD, November 2011 PBAC Meeting).

4.2 MPKU is the condition when a woman who has PKU is pregnant. During pregnancy, the Phe levels affect both the mother and the developing foetus, irrespective of whether the foetus has PKU or not, because Phe crosses the placenta by active transport, resulting in a 70% to 80% increased foetal concentration of Phe compared to the maternal levels (Howard et al., 2008).

4.3 The treatment goal for MPKU is to lower blood Phe levels to the recommended target range. The Australasian MPKU Guidelines recommend maintaining blood Phe in the range of 70-250 µmol/L for 3 months prior to conception and for the duration of the pregnancy (Inwood et al., 2015). High blood Phe levels are teratogenic to the foetus and may result in serious birth defects such as low birth weight, microcephaly, congenital heart disease, facial dysmorphia and intellectual impairment (Lenke and Levy, 1980, Koch et al., 2000, Lee et al., 2003, Prick et al., 2012, van Wegberg et al., 2017). The frequency of these birth defects and intellectual impairment correlates with maternal blood Phe levels (Lenke and Levy, 1980, Prick et al., 2012, Rouse et al., 1997).

4.4 The minor resubmission presented evidence from several sources to suggest that: better outcomes were achieved if patients with PKU managed to reduce their Phe levels to within the target range prior to conception, rather than in early pregnancy; that there is a linear, dose-dependent relationship between the uncontrolled blood Phe levels during pregnancy and negative effects on the cognitive development in offspring; and that apart from sapropterin, the only treatment option is a lifelong protein (Phe) restricted diet which is extremely difficult to adhere to, with non-compliance rates of up to 80% in the overall PKU population. The resubmission argued that the birth defects and intellectual impairments associated with unmanaged MPKU carry a life-long burden of disability, and therefore the unmet clinical need is much higher in pregnant women because of the difficulty in reaching and maintaining the recommended stringent Phe target levels for at least 3 months prior to conception and throughout the entire pregnancy.

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

5 Comparator

5.1 The minor resubmission nominated a Phe-restricted diet as the main comparator, considering it is the only available treatment for adults with MPKU who are not already taking sapropterin. The PBAC considered this was appropriate and consistent with the previous submission for PKU.

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (35), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the benefits of sapropterin treatment during pregnancy, highlighting the additional burden on the mother to strictly manage Phe level prior to conceiving and during pregnancy. The comments also described the difficulty in managing Phe levels after birth due to the lack of time while caring for a newborn and the mental health impacts of high Phe levels in the post-natal period including the increased risk of post-natal depression.

6.3 A large number of comments were also received highlighting the need for equity of access to sapropterin for any adult with PKU and describing a range of benefits of treatment with sapropterin including improvements in neurological function, the positive impact on mental health, the ability to study and to maintain stable employment, the ability to enjoy a near normal diet and enhance social inclusion, and many other benefits pertaining to an improved quality of life. The comments also expressed concern that, should listing be restricted to women who are actively trying to conceive, then women with PKU who have an unplanned pregnancy may be exposed to the teratogenic effects of high Phe levels.

6.4 The PBAC noted the advice received from Rare Voices Australia (RVA) and the Metabolic Dietary Disorders Association (MDDA). The PBAC specifically noted the advice that the use of sapropterin may significantly reduce the burden of treatment on pregnant women, improve their quality of life, and support better pregnancy outcomes. The MDDA stated that high Phe levels in the post-partum period expose mothers to higher risks of post-natal depression, anxiety and poorer executive function for an extended period after the birth of the child. The MDDA suggested that consideration be given to allowing sapropterin use for at least six months post-partum to provide the mother with an opportunity to adjust to motherhood before returning to restrictive, time consuming and expensive dietary therapy. Further, the MDDA stated that its position is that sapropterin should be PBS-subsidised for all patients with PKU. MDDA and RVA advised that listing for only MPKU highlights the inequity of restricting access to specific subsets of a patient community.

6.5 Members of the PBAC met with clinicians prior to the PBAC meeting to discuss the proposed restriction and the practical implementation in the MPKU population. The clinicians highlighted issues including:

- conducting responsiveness testing in the immediate pre-conception phase and the risks of conducting Phe-load testing in pregnant women;
- the total duration of treatment did not allow for extenuating circumstances in which conception may not occur within 12 months;
- the mental health impacts on the mother by ceasing treatment immediately following the birth of the child.

The clinicians were opposed to the narrow population proposed in the submission and supported PBS listing of sapropterin for any adult with PKU. Advice from this discussion informed the PBAC's consideration at the November 2020 meeting.

Clinical evidence

6.6 The minor resubmission presented clinical evidence from dedicated sub-registries of two larger registries: the Kuvan Adult Maternal Paediatric European Registry (KAMPER) and the Phenylketonuria Developmental Outcomes and Safety (PKUDOS) registry.

6.7 While KAMPER and PKUDOS were presented in the March 2018 submission, data specific to the subset of patients with MPKU were not presented in detail.

6.8 Details of the evidence presented in the submission are provided in the table below.

Table 3: Registries presented in the submission

Registry	Protocol title/publication title	Publication citation
Clinical Registries		
Entire PKU Population (data cut June 2013) (PKUDOS)	A voluntary, multi-centre, observational program for patients with PKU in the United States (US) who were receiving, had received, or intended to receive sapropterin within 90 days of entering the registry. 1,224 patients in the US were enrolled in the registry, and 1,189 were eligible for analysis. Patients were not required to be sapropterin responsive to be eligible for PKUDOS.	Longo et al., 2015
PKU-MOMS (data cut June 2013) (PKUDOS)	Data from 21 pregnancies in women with PKU who were treated with sapropterin either before (N = 5) or during (N = 16) pregnancy.	Grange et al. (2014)*
PKU-MOMS (data cut December 2018) (PKUDOS)	Data from 65 pregnancies in 51 women with PKU who were treated with sapropterin.	BioMarin data on file
Entire PKU Population (data cut January 2017) (KAMPER)	A voluntary, multi-centre, multi-national, observational program in Europe that tracked the outcomes of sapropterin therapy in patients with HPA due to PKU or BH4 deficiency. Patients were required to be sapropterin responsive to be eligible for KAMPER and data were only collected for patients while they were treated with sapropterin with the primary objective of KAMPER being to assess the long-term safety of sapropterin. KAMPER provided data for continuous use of sapropterin for up to 6 years (n = 575; 7th interim analysis).	7th interim analysis report) (BioMarin, 2017
KAMPER maternal sub-registry (data cut January 2017) (KAMPER)	A maternal sub-registry of [redacted] female patients who reported as pregnant at enrolment. A total of [redacted] pregnancies were reported, with [redacted] patient reporting [redacted] pregnancies.	Section 10.6.3.4, 7th interim analysis report* (BioMarin, 2017)
KAMPER maternal sub-registry (data cut January 2019) (KAMPER)	There were [redacted] pregnancies reported in [redacted] patients who were either pregnant at enrolment or became pregnant, which corresponds to one additional pregnancy since the 7th interim analysis.	BioMarin data on file

Source: Section 2 of the submission

6.9 PKUDOS is a multi-centre, observational study of patients with PKU in the United States who were receiving, had received, or intended to receive sapropterin within 90 days of entering the registry. Patients were not required to be sapropterin responsive to be eligible for PKUDOS.

6.10 KAMPER is a voluntary, multi-centre, multi-national, observational program in Europe that tracks the outcomes of sapropterin treatment in patients with HPA due to PKU or BH4 deficiency. Patients were required to be sapropterin responsive to be eligible for KAMPER and data were only collected for patients while they were treated with sapropterin. The primary objective of KAMPER was to assess the long-term safety of sapropterin. KAMPER provides data for continuous use of sapropterin for up to 6 years (n = 575; 7th interim analysis).

Comparative effectiveness

<u>Sapropterin in the overall PKU population</u>

6.11 The minor resubmission claimed that sapropterin is associated with the same benefits in terms of reduction in blood Phe levels and increased dietary Phe intake in the MPKU population as in the overall PKU population, and thus reported the results of the two registries for the overall PKU populations.

6.12 In the PKUDOS registry (overall PKU population), the subgroup of patients continuously treated with sapropterin (n = 504) showed an average 34% decrease in blood Phe from a pre-sapropterin baseline of 591 µmol/L (standard deviation (SD): 382) to 392 µmol/L (SD: 239) after 5 years, which was statistically significant (p = 0.0009). These patients increased their dietary Phe intake from 1,000 mg/day (pre-sapropterin exposure) to 1,539 mg/day after 6 years from baseline, and despite the increase, the reductions in blood Phe concentrations were sustained.

6.13 In the KAMPER registry (overall PKU population), the mean blood Phe levels of patients decreased from pre-sapropterin baseline to below 600 µmol/L for most of the time-points up to 6 years, noting that the target range is 120-600 µmol/L in Europe in non-pregnant patients over the age of 12 years. At baseline (pre-sapropterin), the mean Phe level was 609.8 µmol/L, which reduced to 468.4 µmol/L at 1 year. The dietary Phe intake and natural protein intake increased from pre-sapropterin baseline and this was sustained over 6 years while patients' blood Phe levels remained within the target range for almost all time points.

<u>Sapropterin in the MPKU population</u>

6.14 Two data-cuts of the PKU-MOMS sub-registry were presented: June 2013 and December 2018. While the later data-cut included data from a larger number of pregnancies, more detailed information regarding clinically relevant pregnancy outcomes were provided for the June 2013 data-cut.

6.15 The June 2013 data-cut of the PKU-MOMS sub-registry contained data from 21 pregnancies in women with PKU, five of whom were treated with sapropterin before pregnancy (but not during pregnancy), and 16 of whom were treated with sapropterin during pregnancy. Individual patient data is presented in the table below.

Table 4: Blood Phe levels, dietary Phe intake, and pregnancy outcome in PKU-MOMS

ID	Age, years	Highest lifetime Phe (µmol/L)	Sapropterin dose during pregnancy mg/kg	Time on sapropterin, days	Median Phe during pregnancy (µmol/L)	Phe > 360 µmol/L, %	Phe < 120 µmol/, %	Median actual Phe intake	Pregnancy outcome [a]
Women who received sapropterin prior to pregnancy									
1	34	1,464	-	-	615	100.0	0.0	420	Normal
2	23	900	-	-	205	0.0	0.0	1,050	SAB
3	30	2,400	-	-	85	7.7	69.2	425	Normal
4	31	2,400	-	-	42	25.0	75.0	NA	SAB; absent yolk sac
5	32	2,400	-	-	103	3.4	51.7	750	Normal
Women who received sapropterin during pregnancy									
6	29	1,572	19	293	157	0.0	21.4	1,000	Normal [b]
7	34	NA	7	992	206	21.2	14.1	287	Normal
8	36	NA	7	1,372	842	100.0	0.0	NA	SAB
9	23	1,026	20	1,925	115	24.0	52.0	550	Normal
10	18	480	10	888	224	0.0	0.0	1,761	Abnormal; SGA [c]
11	31	1,908	20	1,410	496	78.3	0.0	246	Normal
12	27	1,200	20	2,012	118	6.1	51.5	NA	Normal
13	23	978	20	345	203	3.1	9.4	NA	Normal
14	33	1,200	20	2,096	148	2.8	2.8	NA	Normal
15	31	1,062	10	673	121	0.0	48.4	1,800	Abnormal; hypo-phagia and prematurity (34w4d)
16	22	1,650	20	737	186	15.2	18.2	NA	Normal
17	18	792	20	348	154	0.0	16.7	NA	Normal
18	38	600	15 [e]	227	484	54.5	0.0	3,501	Abnormal; bilateral cleft palate[d] and poor feeder
19	41	3,060	5	1,446	378	100.0	0.0	NA	SAB [f]
20	32	NA	20	831	157	0.0	10.0	3,000	Normal
21	29	1,158	20	1,663	97	0.0	77.4	NA	Normal

Source: Table 2-5 of the minor resubmission

Phe: phenylalanine; NA = not available or not applicable; SAB: spontaneous abortion

[a] Pregnancy outcome as determined by the condition at birth, birth anthropometric values and adverse events at birth.

[b] Offspring 6 had normal anthropometric measurements but was diagnosed with PKU.

[c] Offspring 10 was Small for Gestational Age (SGA), due to weight below 3rd percentile.

[d] For pregnancy 18, sapropterin was started at 8w6d gestation; 7 mg/kg/day for 3 days; and 15 mg/kg/day for the rest of the pregnancy.

[e] Offspring 18 — The cleft palate was reported in the sub-registry as "bilateral cleft palate"; no lip involvement was present.

[f] The ultrasound for pregnancy 19 was abnormal, with a very small cardiac sac — (a condition associated with foetal mortality).

6.16 Excluding data for spontaneous abortions (n = 4), the data show that the mean of the median blood Phe levels (204.7, SD: 126.6 µmol/L; n = 14) for women treated with sapropterin during pregnancy was 23% lower and had a 58% smaller standard

deviation compared with the blood Phe (267.4, SD: 300.7 µmol/L; n = 3) for women who were not treated with sapropterin during pregnancy (i.e. treated prior to pregnancy group). Women on sapropterin during pregnancy experienced fewer blood Phe values above 360 µmol/L. When median blood Phe concentration was < 360 µmol/L throughout pregnancy, 75% (12/16) of pregnancy outcomes were normal versus 40% (2/5) of pregnancy outcomes when the median blood Phe was > 360 µmol/L.

6.17 The December 2018 data-cut of the PKU-MOMS sub-registry included data from 51 women reporting 65 pregnancies (several patients remained in the study throughout multiple pregnancies) with a mean sapropterin exposure during pregnancy of 248 days (SD: 51; n = 45) (BioMarin, data on file). The mean sapropterin dose was 18.7 mg/kg/day prior to pregnancy (SD: 3.8; n = 58), 18.0 mg/kg/day during pregnancy (SD: 3.9; n = 45), and 18.6 mg/kg/day after pregnancy (SD: 3.1; n = 51). Mean blood Phe was 486 µmol/L (SD: 319; n = 56) prior to pregnancy, 291 µmol/L (SD: 170; n = 60) during the 1st trimester, 235 µmol/L (SD: 167; n = 55) during the 2nd trimester, and 195 µmol/L (SD: 140; n = 46) during the 3rd trimester.

6.18 The following birth outcome data were available for the December 2018 data-cut (reported as adverse event data):

- Of eight pregnancies which ended in spontaneous abortion, six had at least one episode of maternal blood Phe > 360 µmol/L recorded during pregnancy.
- Of 45 pregnancies with birth outcome data available, 41 were reported as normal and four were reported as abnormal. The four abnormal birth outcomes reported were one incident each of microcephaly, cleft palate, tongue tie, and premature birth (35 weeks 3 days gestation); all four of these mothers received sapropterin during gestation. The two serious abnormal outcomes (microcephaly, cleft palate) both resulted from pregnancies in which blood Phe was above target range during the 1st trimester. At birth, and at 1- and 6-month infant follow-up visits, there were no additional related AEs or SAEs.

6.19 At the January 2017 data-cut of KAMPER, [redacted] women participated in the KAMPER maternal sub-registry, with a total of [redacted] pregnancies being reported ([redacted] patient reported [redacted] pregnancies). Of the [redacted] pregnancies with available data, all [redacted] resulted in full term live birth deliveries, with all infant conditions at birth reported as normal.

6.20 At the January 2019 data-cut of KAMPER, data from [redacted] additional pregnancy were available. The mean age at delivery was 29.6 (SD: 3.8; range: 23.3-35.5) years. The sapropterin dose was constant prior to, during, and after pregnancy, with a median dose of 10.0 mg/kg/day; the mean duration of exposure during pregnancy was 270.4 days (SD: 14.2). Maternal blood Phe concentrations were either within the clinical range (120-360 µmol/L, n = [redacted]) or high (>360 µmol/L, n = [redacted]) during the 1st trimester of pregnancy, were within the clinical range (n = [redacted]) during the 2nd trimester,

and were either within the clinical range (n = [redacted]) or low (< 120 µmol/L, n = [redacted]) during the 3rd trimester.

Comparative harms

6.21 In the June 2013 data cut of the PKU-MOMS sub-registry, a total of 62 maternal unique AEs occurred in 72% (13/18) of women. Most (82%, 51/62) maternal AEs were reported as unrelated to sapropterin. The AEs that were possibly related included: premature labour, spontaneous abortion, joint pain, jaw pain, swelling (fingers or toes), pre-diabetes, nausea, vomiting, short-term memory loss, and heartburn. Two of the 11 possibly related AEs were reported as serious adverse events (SAEs): premature labour and spontaneous abortion. Sapropterin was not discontinued in any of the pregnancies. Of the four spontaneous abortions reported in the sub-registry, two occurred in women exposed to sapropterin during pregnancy (12.5%, 2/16) and two in women exposed to sapropterin prior to (but not during) pregnancy (40%, 2/5). The two in the group exposed to sapropterin during pregnancy occurred between 8 and 10 week gestational ages, the sapropterin dose was 5-7 mg/kg/day, and both had other risk factors (i.e. advanced maternal age, prior history of spontaneous abortion, poorly controlled PKU, abnormal ultrasound, and/or other drug (Category C and D) exposure).

6.22 In terms of adverse events in offspring, the PKU-MOMS sub-registry recorded 11 unique AEs that occurred in 33% (1/3) of offspring born to women exposed to sapropterin prior to pregnancy, and 42.8% (6/14) of offspring born to women exposed to sapropterin during pregnancy. One AE was reported as possibly related to sapropterin (hypophagia SAE, which resolved in 9 days). The other 10 AEs were reported to be unrelated to sapropterin and 55% were mild.

6.23 At the December 2018 data cut, 193 AEs had been reported, and 23 were assessed as related to sapropterin, including three which were considered serious (one premature labour and two spontaneous abortions). The other non-serious AEs reported were nausea, dyspepsia, vomiting, amnesia, headache, peripheral swelling, swelling, impaired glucose tolerance, arthralgia, and jaw pain.

6.24 In the PKU-MOMS sub-registry (December 2018 data-cut), of [redacted] pregnancies that ended in spontaneous abortion, [redacted] had at least one episode of maternal blood Phe ≤ 30 µmol/L recorded during pregnancy (the other [redacted] had at least 1 episode of maternal blood Phe > 360 µmol/L). Of [redacted] infants who were born alive and who were exposed to at least one episode of maternal blood Phe ≤ 30 µmol/L during gestation, all birth outcomes were normal.

6.25 At the January 2017 data-cut of the KAMPER maternal sub-registry, eight AEs were reported in [redacted] patients while pregnant. These AEs were mild hyperthyroidism, surgical/diagnostic procedure, mild upper respiratory tract infection, mild cytomegalovirus infection during labour, moderate arrhythmia, mild tooth injury, mild dyspepsia, and cobalamin deficiency. None of these AEs were considered related to

sapropterin. The patients who experienced AEs while pregnant had normal full-term births. Two AEs (jaundice and ocular icterus) were reported for one of the infants. Both AEs were considered mild in severity and unrelated to sapropterin.

6.26 At the January 2019 data cut, there had been no additional safety outcomes reported.

Clinical claim

6.27 The minor resubmission claimed that sapropterin is associated with the same benefits in terms of reduction in blood Phe levels and increased dietary Phe intake in the MPKU population as in the overall PKU population.

6.28 The minor resubmission claimed that in patients with MPKU, sapropterin in combination with a Phe-restricted diet is more effective than a Phe-restricted diet alone at reducing blood Phe levels and increasing dietary Phe intake.

6.29 The minor resubmission claimed that sapropterin has an acceptable safety profile in pre-conception and pregnancy.

6.30 The PBAC noted that the evidence provided was limited, but considered that the claims of superior comparative effectiveness and non-inferior comparative safety were both reasonably supported by the data. However, the PBAC considered the magnitude of the benefit was difficult to quantify, particularly for patient relevant outcomes (such as pregnancy outcome, birth defects and cognitive development in offspring).

Economic analysis

6.31 Unchanged from the November 2018 minor submission, the submission presented a cost-utility analysis against: 'a relaxed or abandoned diet' for patients with poorly-controlled blood Phe-levels; and against 'a strict Phe-restricted diet' for those with well-controlled blood Phe levels. Separate incremental cost effectiveness ratios (ICERs) were calculated for each of the subpopulations (the 'poorly-controlled Phe level' group and the 'well-controlled Phe level' group). These were combined in a weighted analysis for the base-case economic evaluation.

6.32 The key changes compared with the economic model submitted in the previous submission were:

- While the previous submission calculated ICERs for each age between 0 and 17 years and one for ≥ 18 years, with a one year time horizon for each age group, this submission used a time horizon of [redacted] months (i.e. the treatment duration of [redacted] months excluding the [redacted] of sapropterin responsiveness testing, which was proposed to be rebated in an RSA) and was based on patients ≥ 18 years of age.
- The average dose was assumed to be 20 mg/kg (the maximum dose), while the previous submission assumed a dose of 17.4 mg/kg based on the mean dose across four different studies.

- Minor updates (e.g. to reflect current mark-ups, availability of sapropterin 500 mg).

6.33 The resubmission included a pricing proposal that was consistent with the current RSA for sapropterin, which was based on capping the cost of sapropterin treatment for [redacted].

6.34 Unchanged from the November 2018 minor submission, the following assumptions were made:

- 33% of patients were assumed to be controlled on a Phe-restricted diet while the remaining 67% of patients were assumed to be uncontrolled. Of the uncontrolled cohort, 45% were assumed to follow a relaxed Phe-restricted diet and 55% had abandoned the Phe-restricted diet.
- Compliance with Phe-free amino acid supplements for patients on a strict, relaxed, and abandoned Phe-restricted diet continued to be assumed to be 100%, 50% and 0%, respectively. For patients treated with sapropterin, the analysis included a 31% reduction in Phe-free amino-acid supplements for those who were previously well controlled on a Phe-restricted diet.
- The utilities for patients treated with sapropterin, controlled on a Phe-restricted diet, uncontrolled on a relaxed Phe-restricted diet and uncontrolled due to diet abandonment were 0.71, 0.59, 0.48 and 0.37, respectively.

6.35 The results of the economic evaluation are shown in the table below. As a minor submission, the economic model was not independently evaluated.

Table 5: Results of the economic evaluation

	Cost			Outcomes			$/QALY
	Sapropterin	Phe-restrict. diet only	Incr.	Sapropterin	Phe-restrict. diet only	Incr.	
Overall MPKU population (weighted ICER)							
MPKU	$[redacted]	$[redacted]	$[redacted]	1.29	0.86	0.42	**$**[redacted][1]
ICERs for the two subpopulations							
Uncontrolled PKU: Sapropterin + relaxed/abandoned Phe-restricted diet vs. Relaxed/abandoned diet. **67% weighting**							
MPKU	$[redacted]	$[redacted]	$[redacted]	1.29	0.76	0.53	$[redacted][2]
Controlled PKU: Sapropterin + relaxed Phe-restricted diet vs. Phe-restricted diet**. 33% weighting**							
MPKU	$[redacted]	$[redacted]	$[redacted]	1.29	1.07	0.22	$[redacted][3]
Previous submission (various ages are presented to provide indication of ICER ranges; 1 year time horizon)							
≥18 years: assumed 33% were in the well-controlled group (assuming patient weight of 78.4 kg)							$[redacted][a,1]
0 years: assumed 82% were in the well-controlled group							$[redacted][4]
5 years: assumed 82% were in the well-controlled group							$[redacted][5]
10 years: assumed 82% were in the well-controlled group							$[redacted][2]

Source: Table 3-1of the minor resubmission; 'Kuvan (sapropterin) - Economic evaluation.xlsx' worksheet 'economic evaluation'; Table 2, November 2019 Minutes for sapropterin.

[a] The reason the ICER in MPKU patients is lower than that previously estimated for patients aged ≥ 18 years is due to the lower patient weight assumed in the current submission ([redacted]kg versus [redacted] kg). The assumption of a lower patient weight is based on the rebates proposed in the RSA. Further, the current submission also assumed an average dose of 20 mg/kg (the maximum dose), while the previous submission assumed a dose of 17.4 mg/kg.

The redacted values correspond to the following ranges

[1] *$355,000 to < $455,000*

[2] *$255,000 to < $355,000*

[3] *$655,000 to < $755,000*

[4] *$55,000 to < $75,000*

[5] *$155,000 to < $255,000*

6.36 The submission estimated a weighted ICER for sapropterin of $355,000 to < $455,000/QALY. The ICERs for the two subpopulations were estimated to be: $255,000 to < $355,000/QALY for patients who are uncontrolled on a relaxed or abandoned diet (weighted 67%); and $655,000 to < $755,000/QALY for those who are controlled on a strict Phe-restricted diet (weighted 33%).

6.37 In the previous submission, the ICER ranged from $55,000 to < $75,000/QALY for patients aged less than one year to $555,000 to < $655,000 /QALY for those aged 17 years. The ICER/QALY was $155,000 to < $255,000 for a patient who commences sapropterin at birth and continues 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 are well controlled (in which sapropterin is assumed to be less cost-effective) decreases after the age of 17.

6.38 The economic analysis included the impact of rebates which it proposed would be achieved through an RSA. These rebates will only be realised if utilisation levels are higher than the levels agreed in the RSA. Without these rebates, the ICER would be $355,000 to < $455,000/QALY if an average patient weight of [redacted]kg is assumed (per the financial estimates). The existing RSA utilisation cap for sapropterin is not currently

being reached, with utilisation in Year 1 (May 2019 - April 2020) being at [redacted]% of the level of the agreed cap, indicating that utilisation has been lower than estimated. As a joint cap will likely be required due to the overlapping populations, the rebates for patient weight in the MPKU population may not be realised if the current caps are not adjusted to align with actual utilisation.

6.39 The economic analysis assumed an average dose of 20 mg/kg and 100% compliance. Assuming an average dose of 18 mg/kg (based on PKU-MOMS 2018 data-cut) and 80% compliance (per the financial estimates) would reduce the ICER to $255,000 to < $355,000/QALY. In this same scenario, but without the rebate based on patient weight, the ICER would be $255,000 to < $355,000/QALY.

6.40 The economic model assumed the sponsor would rebate all doses used for initial responsiveness testing. The ICER would be higher if the Commonwealth funds any doses used for this purpose. The rebate for initial responsiveness testing could be applied as an SPA rebate (rather than through RSA caps) to provide greater certainty these rebates will apply.

6.41 In its previous consideration, the PBAC "considered that the incremental cost-effectiveness ratio estimated in the resubmission was high, the Committee acknowledged the high clinical need in this small patient group and considered that the clinically significant outcomes in patients under the age of 18 may not have been fully captured in the economic evaluation" (para 6.10, sapropterin PSD, November 2018 PBAC meeting).

6.42 The economic analysis presented in the submission 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. As such, the key clinically significant outcome in the MPKU population was not fully captured in the economic evaluation.

6.43 The economic analysis assumed that 67% of patients had uncontrolled PKU (and therefore had poor quality of life, with utility values between 0.37 and 0.48), which was based on patients aged ≥ 18 years being less likely to have adequately controlled PKU. However, it is unknown if this assumption is applicable to pregnant women (or women trying to conceive), who may be more motivated to have well-controlled PKU levels than the broader adult PKU population (given the severe consequences of uncontrolled PKU during pregnancy). Sapropterin is significantly less cost-effective in patients whose PKU is already well-controlled.

6.44 While the ICER is calculated based on a [redacted] month time horizon, the results do not change with differing durations of therapy because the costs and outcomes per month are constant.

Drug cost/patient/course (22 months)

6.45 In the economic analysis, the submission estimated that the cost of sapropterin per patient per 22 month course would be $[redacted]. This was based on an average dose

of [redacted] mg per day (20 mg/kg, average patient weight of [redacted] kg), requiring <500 scripts of the 500 mg powder (qty 30) and <500 scripts of the 100 mg soluble tablets (qty 180 per script), and assuming the sponsor will rebate the cost of all doses used for initial responsiveness testing. No compliance assumptions were included in the economic analysis.

6.46 The financial estimates assumed 80% compliance, and thus the cost per patient per course was $[redacted] (including the proposed rebate for initial responsiveness testing and with caps based on an average patient weight of [redacted] kg).

6.47 The submission assumed that patients treated with sapropterin would use less subsidised Phe-free amino acid supplements ($4,460 less over the [redacted] month treatment course in the economic analysis).

Estimated PBS usage & financial implications

6.48 The submission used an epidemiological approach to estimate the financial implications of listing sapropterin for MPKU.

6.49 The submission estimated the number of births in Australia per year over six years (based on ABS data), then applied the following epidemiological assumptions which were unchanged from the previous submission:

- the prevalence of HPA was assumed to be 1:11,266 (based on Bonah, et al 2006)
- 98.8% of PKU was assumed to be due to HPA (based on Abadie et al, 2001)

6.50 Other key assumptions are outlined in the table below.

Table 6: Key assumptions in the financial estimates

	November 2018 resubmission	Current resubmission
Eligible for treatment	65% (restriction requires Phe >360 µmol/L in newborns and >600 µmol/L in all other patients)	95% followed-up in clinic (assumption, no source stated), noting the requested restriction requires Phe >250 µmol/L
Uptake rate	75%	85% (assumption, no source stated)
% who respond	50%	50% (unchanged)
Dose forms	Sapropterin 100 mg tablets	Sapropterin 100 mg tablets and 500 mg powder[a]
Dose	17.43 mg (weighted mean dose across 4 studies)	20 mg/kg, based on the maximum recommended dose (assumption, no source stated). PKU-MOMS December 2018 data reported an average dose of 18 mg/kg during pregnancy.
Body weight	For patients ≥ 18 years of age: • 78.4 kg (average weight for 18+, all genders) • For RSA: [redacted] kg	• 71.1 kg (average female weight for 18+) • For RSA: [redacted] kg (average weight at [redacted], all genders)
Compliance	80%	80% (unchanged)
Treatment duration	On-going	[redacted] months (average, i.e. all patients were assumed to be treated for a full [redacted] months)

Source: Financial estimates spreadsheet for current submission and Nov 2018 pre-PBAC response.

[a] 500mg powder recommended for listing by PBAC at the July 2019 meeting

6.51 The table below summarises the financial implications of listing sapropterin for MPKU.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated – initiating	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients treated – continuing	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts[a] – responsiveness testing	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts[a] – maintenance	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total no. scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of sapropterin						
Cost to PBS/RPBS less co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Rebates proposed in RSA						
Rebate for weight	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Rebate for responsiveness testing	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Estimated financial implications for PKU supplements (PKU cooler)						
Cost to PBS/RPBS less co-payments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Total rebates	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
RSA caps	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
RSA caps less offsets for PKU cooler	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

[a] Assuming 12.7 * 100mg scripts (qty 180) and 35.7 * 500 mg scripts (qty 30) per patient per [redacted] month course (split over 2 years) as estimated by the submission.

The number of scripts for responsiveness testing was based on part scripts (i.e. the submission assumed that patients undergoing responsiveness testing would each receive 0.26 of a script for the 100 mg strength, and 0.37 of a script for the 500mg strength). This would underestimate the rebate, as patients who do not meet the responsiveness criteria would not use the remainder of the tablets dispensed (wastage).

Source: Table 4-2 of the submission; financial estimates spreadsheet for current submission

The redacted values correspond to the following ranges

[1] *<500*

[2] *500 to <5,000*

[3] *$0 to < $10 million*

6.52 The cost to the PBS/RPBS for sapropterin (excluding offsets for reduced use of Phe-free amino acid supplements) was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million over 6 years. Including the impact of offsets and rebates, the estimated cost to the PBS/RPBS is $0 to < $10 million over 6 years.

6.53 As a minor submission, the financial estimates have not been independently evaluated. However, a number of minor issues were noted:

- The estimates assumed that all patients who respond will use [redacted] months of treatment (per birth), however some patients may require a shorter or longer duration of treatment.

- Should the initial restriction allow responsiveness testing in all women of child-bearing age: uptake of initial responsiveness testing would be higher than estimated; and there would be a high risk of usage in patients outside the intended population once responsiveness has been established. Alternatively, uptake of the continuing restriction may be lower than estimated initially as clinicians may be reluctant to perform responsiveness testing (which requires a Phe load to be administered) in pregnant women or women actively trying to conceive, due to the potential teratogenic effects of a Phe load during this period.
- The estimates were based on all patients receiving a dose of 20 mg/kg, which is the maximum dose (recommended dose is 5 mg/kg to 20 mg/kg). The previous submission applied a dose of 17.4 mg/kg (based on the average dose in study evidence). The PKU-MOMS data presented in the submission indicated an average dose of 18 mg/kg during pregnancy in the December 2018 data-cut. The pre-PBAC response stated that all MPKU patients were assumed to be maintained on the maximum dose due to the importance of reaching and maintaining blood Phe levels of 120-250 µmol/L in MPKU.
- The estimates were based on the prevalence of HPA in the general Australian population. It is unknown if this prevalence rate will be the same in women actively trying to conceive.

Financial Management – Risk Sharing Arrangements

6.54 The submission proposed a [redacted]% rebate on the cost to the PBS of all sapropterin used for initial responsiveness testing. The submission also based the proposed caps on the utilisation required for a patient who weighs [redacted] kg.

6.55 The submission proposed that PBS/RPBS expenditure would be capped at the estimates outlined in Table 7 (based on the "RSA cap" row) with a [redacted]% rebate to expenditure above this level. The proposed RSA cap was $[redacted] over five years.

6.56 The PBAC considered that an RSA with a [redacted]% rebate on expenditure above the caps was required given the significant risk of leakage in women who are not actively trying to conceive and the risk of use for a prolonged treatment duration.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation to list sapropterin in combination with a phenylalanine (Phe)-restricted diet for the treatment of maternal phenylketonuria (MPKU) in order to consult further on the appropriate restriction, particularly: eligibility and processes for initial responsiveness testing; defining the circumstances of use post-partum; and defining the most equitable duration of therapy. As part of

the deferral, the PBAC requested the sponsor provide further information regarding the feasibility of the proposed restriction for clinicians in practice.

7.2 The PBAC considered there was a particularly high clinical need for sapropterin in patients with MPKU given the potential impact of high Phe levels on the unborn child and the difficulty in reaching and maintaining the recommended stringent Phe target levels in this population. The PBAC acknowledged the input received from individuals, organisations and health professionals.

7.3 The PBAC also 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. The PBAC noted that limiting subsidy to the MPKU population reduces equity in access and creates potential for use outside the circumstances considered cost-effective. However, at the price proposed in the submission and from the information available, the PBAC did not consider it cost-effective to list sapropterin for any adult with PKU.

7.4 The PBAC noted that initial responsiveness testing often involves a pre-test Phe load, but that high blood Phe levels are teratogenic to the foetus. Guidelines also recommend maintaining blood Phe in the range of 70-250 µmol/L in the 3 months prior to conception. The PBAC considered that clinicians will likely be reluctant to perform responsiveness testing during pre-conception and pregnancy and considered that load testing should optimally occur before the pre-conception period. Rather than restricting testing to women who are actively planning to conceive, the PBAC noted an alternative option could be to allow all women of child-bearing age to undergo initial responsiveness testing to determine suitability for commencement of longer-term sapropterin treatment at a later time-point, when/if they conceive or actively try to conceive. However, the PBAC considered that this would lead to an increased risk of patients continuing treatment outside the intended PBS restriction, and unnecessary pressure on clinicians to withhold a treatment to which they knew the patient would be responsive. As part of the deferral process, the PBAC requested further consultation with the sponsor regarding eligibility and processes for initial responsiveness testing.

7.5 The PBAC considered the requested maximum treatment duration of 22 months potentially insufficient for some patients, noting that:

- guidelines state that patients should maintain blood Phe in the range of 70-250 µmol/L for at least the 3 months prior to conception, and that it can take 3-6 months to achieve regulated Phe levels, especially in sapropterin naïve patients;
- conception time is variable ;

- treatment should be continued for the full term of the pregnancy; and

The PBAC considered that it may be appropriate for some patients to remain on therapy in the initial post-partum period.

7.6 The PBAC considered that the restriction should provide sufficient flexibility to allow longer treatment durations in specific, defined circumstances. Such circumstances may include patients: (a) whose blood Phe takes a prolonged period to stabilise within the required range; (b) who experience fertility issues (noting that there are many treatment options for infertility and exploring these options has no definitive timeframe); and/or (c) who are considered to be at risk of adverse mental health effects if treatment is ceased immediately post birth. However, the PBAC considered that enabling clinician determined treatment duration will increase the risk of usage beyond the intended circumstances of use. As part of the deferral process, the PBAC requested further consultation with the sponsor regarding the most appropriate balance between an unlimited PBS-subsidised treatment duration versus a set, predetermined amount, as well as the specific circumstances in which use post-partum would be appropriate.

7.7 The PBAC noted that the requested listing was similar to the prescribing criteria in place in New Zealand. The PBAC requested that the sponsor provide further information regarding any clinician or stakeholder feedback on the New Zealand experience, along with information regarding the uptake and utilisation of sapropterin in patients with MPKU in New Zealand.

7.8 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.

7.9 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, given the teratogenic effects of high Phe levels. Unmanaged PKU can be teratogenic leading to birth defects (e.g. microcephaly, congenital heart disease, facial dysmorphia, low birth weight) and intellectual impairment in offspring which can carry a life-long burden of disability.

7.10 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. As such, the PBAC considered that key clinically significant outcomes in the MPKU population (e.g. birth defects and intellectual impairment in offspring) were not captured in the economic analysis, and acknowledged the difficulties in assessing cost-effectiveness in this patient group. Overall, the PBAC considered that sapropterin was likely to be cost-effective in this small population given the likely significant clinical benefits in MPKU.

7.11 The PBAC noted that the financial estimates assumed that all patients who respond to sapropterin will use [redacted] months of treatment (per birth). The PBAC considered that it would be appropriate to assume an average [redacted] month treatment duration if the restriction were to allow use for longer than [redacted] months in specific circumstances, given there would still be a proportion of patients who may use sapropterin for a shorter duration.

7.12 Overall, the PBAC considered that the financial estimates were reasonable and reflected likely utilisation in the intended population.

7.13 The PBAC noted that the submission proposed a [redacted]% rebate on expenditure above the proposed caps (which were based on the patient numbers estimated in the submission and capping the cost of sapropterin treatment for patients aged ≥ 18 years to that of a patient aged 17 years) and included a [redacted]% rebate on all sapropterin used for initial responsiveness testing. The PBAC considered this was appropriate given the significant risk of leakage in women who are not actively trying to conceive and the risk of use for a prolonged treatment duration.

7.14 The PBAC noted the strong consumer feedback describing the very high clinical need for access to sapropterin for any adult with PKU. The PBAC would welcome a major resubmission for this broader population. Such a resubmission should address issues raised previously by the PBAC, including that the economic model was not reliable for the broader adult population.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

BioMarin thanks the Committee and acknowledges the ongoing consumer support for broader access to effective treatments for PKU. This recommendation builds upon BioMarin's more than 10-year commitment to the PKU community and we look forward to bringing further therapies for the condition to Australian patients in future.

Addendum to the November 2020 PBAC Minutes:

4.04 SAPROPTERIN

Powder for oral solution 500 mg
Tablet (soluble) 100mg
Kuvan®,
BioMarin Pharmaceutical Australia Pty Ltd

10 Background

10.1 At its November 2020 meeting, the PBAC deferred making a recommendation to list sapropterin in combination with a Phe-restricted diet for the treatment of MPKU in order to consult further on the appropriate restriction, particularly: eligibility and processes for initial responsiveness testing; defining the circumstances of use post-partum; and defining the most equitable duration of therapy. As part of the deferral, the PBAC requested the sponsor provide further information regarding the feasibility of the proposed restriction for clinicians in practice.

10.2 The sponsor was also requested to provide further information regarding any clinician or stakeholder feedback on the New Zealand experience (given the requested listing was similar to the prescribing criteria in place in New Zealand), along with information regarding the uptake and utilisation of sapropterin in patients with MPKU in New Zealand.

10.3 The sponsor stated that the feedback it had received from PHARMAC in New Zealand was that "leakage is not a concern because of the written authority restriction, and the limited treatment duration which acts as a disincentive for non-pregnant women". The sponsor stated "the 22 month treatment duration was developed in consultation with the National Metabolic Service, and PHARMAC has not received any correspondence to suggest that the duration is not suitable".

10.4 The sponsor stated that it also consulted with a metabolic clinician in New Zealand. The sponsor stated that the feedback provided was that "sapropterin is offered to women with PKU who are planning pregnancy if they are unable to achieve satisfactory levels with dietary management…. women are usually able to achieve satisfactory Phe levels within 2-3 months of going onto pre-conception diet, prior to commencing IVF treatment or attempting to conceive, and in [their] experience, women with PKU have a tendency to go back to their usual diet (whether restricted or relaxed) immediately after delivery".

10.5 The sponsor "reconfirm[ed] its commitment to the RSA caps as proposed in the submission, in relation to the [redacted] month duration of treatment."

10.6 In discussions, the sponsor re-iterated its proposal that initial responsiveness testing only be offered to women who are pregnant or actively trying to conceive. The pre-PBAC response from November 2020 had stated that guidelines recommend that patients consult with a metabolic MPKU multidisciplinary team at least 4 months prior to conception and that if the clinician wishes to add a pre-test Phe load, this could be done during this pre-conception period.

11 PBAC Outcome

11.1 The PBAC recommended the Authority Required listing of sapropterin in combination with a phenylalanine (Phe)-restricted diet for the treatment of maternal phenylketonuria (MPKU). The PBAC considered that a treatment duration of 22 months or until cessation of pregnancy would be appropriate, and that initial responsiveness testing should be restricted to patients who are actively planning to become pregnant or who are pregnant.

11.2 The PBAC was satisfied that sapropterin provides, for some patients, a significant improvement in efficacy over a Phe-restricted diet alone.

11.3 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of sapropterin for the treatment of MPKU would be acceptable at the price proposed in the submission in conjunction with the submission's proposed RSA. The PBAC considered that while the estimated ICER is high, the economic analysis presented did not capture the key clinically significant outcomes in the MPKU population (e.g. birth defects and intellectual impairment in offspring), and acknowledged the difficulties in assessing cost-effectiveness in this patient group. Overall, the PBAC considered that sapropterin was likely to be cost-effective in this small population given the likely significant clinical benefits in MPKU.

11.4 The PBAC considered that the appropriate duration of therapy would be up to a maximum of approximately 22 months or until cessation of pregnancy (excluding responsiveness testing, as discussed in the paragraph below). Within these 22 months, the expectation is that PBS-subsidised treatment cover:

- the time taken to achieve Phe level control, noting that the New Zealand prescribing criteria allow one month for this, but clinician feedback has been that control may take longer than 1 month;
- the time taken to conceive (when pregnancy first becomes known would be a proxy for this in practice), noting that the New Zealand prescribing criteria allow 12 months for this; and
- pregnancy (9 months).

11.5 Initial responsiveness testing (conducted over a 7 day period, consistent with the existing listing) would be conducted prior to the 22 month treatment period. The PBAC

considered that initial responsiveness testing should be restricted to patients who are actively planning to become pregnant or who are pregnant. The PBAC considered that the method for responsiveness testing, in terms of whether to include a Phe load, should be at clinician discretion taking patient circumstances into account.

11.6 Unlike sapropterin's existing listing which has a maximum quantity (packs) of 3 for the tablets in responsiveness testing, and 6 packs for continuing treatment, the new indication could have a maximum quantity (packs) of 1 for the tablets in each treatment phase with the expectation that the prescriber request an appropriate increase in quantity at the time of the authority application. This would prevent prescribers from defaulting to the stated value in situations where the stated maximum quantity would provide for a treatment duration of more than the intended 30 days per dispensing (and 7 days for the initial responsiveness testing period).

11.7 The PBAC reiterated that the financial estimates proposed in the submission were reasonable and reflected likely utilisation in the intended population.

11.8 The PBAC noted that the submission proposed a [redacted] rebate on expenditure above the proposed caps (which were based on the patient numbers estimated in the submission and capping the cost of sapropterin treatment for patients [redacted] and included a [redacted] rebate on all sapropterin used for initial responsiveness testing. The PBAC considered this was appropriate given the risk of leakage in women who are not actively trying to conceive and the risk of use for a prolonged treatment duration.

11.9 The PBAC reiterated that it would welcome a major resubmission for sapropterin for all adults with PKU.

11.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not 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 improvement in efficacy over alternative therapies;
b) Treatment with sapropterin is not expected to address a high and urgent unmet clinical need;
c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:

Recommended

12 Recommended listing

12.1 Add new indication (maternal HPA due to PKU) as follows:

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	NEW	1	30	0	Kuvan
sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	NEW (separate from 11971C)	1	30	0	Kuvan
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required – immediate/real time assessment by Services Australia (telephone/online)				
7608	**Administrative Advice:** Special pricing arrangements apply				
25796	**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.				
	Episodicity: Maternal				
	Severity: [blank]				
	Condition: hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)				
NEW (don't use 23976)	**Indication:** Maternal hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)				
	Treatment Phase: Initial treatment – responsiveness testing				
NEW	**Clinical criteria:**				
	The treatment must be for the purpose of ascertaining the patient's response to treatment over a period of 7 days, with the intent to then use the drug to control phenylalanine levels under the treatment phase: 'Pre-conception through to when pregnancy first becomes known'; OR				
NEW	The treatment must be for the purpose of ascertaining the patient's response to treatment over a period of 7 days in an existing, unplanned pregnancy				
	AND				
NEW	**Clinical criteria:**				
	Patient must have a baseline blood phenylalanine level above 250 micromol/L prior to commencing treatment with this drug despite best efforts to rely on dietary modifications to control phenylalanine levels				
11332	**Treatment criteria:**				
11331	Must be treated by a metabolic physician				
	AND				
	Treatment criteria:				
NEW	Patient must be undergoing treatment with this drug for the first time				
	AND				
NEW	**Treatment criteria:**				
	Patient must not be undergoing treatment with this drug under this Treatment phase, more than once per lifetime following completion of this authority application				
	AND				
NEW	**Treatment criteria:**				
	Patient must not be undergoing simultaneous treatment with this drug under another PBS-listing (apply under either listing type, but not both simultaneously)				

NEW	**Administrative advice:** Request an appropriate maximum quantity based on testing response to treatment for 7 days, with the number of packs being a whole number, based on dosing no greater than 20 mg/kg per day. Combinations of the sachets and tablets are permitted to reduce high tablet burden.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.

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	NEW	1	30	5	Kuvan
sapropterin dihydrochloride 500 mg powder for oral liquid, 30 sachets	11983Q	1	30	5	Kuvan

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction Type: ☒ Authority Required – immediate/real time assessment by Services Australia (telephone/online)
7608	**Administrative Advice:** Special pricing arrangements apply
25796	**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.
NEW	**Indication:** Maternal hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: Pre-conception through to when pregnancy first becomes known
	Clinical criteria:
NEW (don't use 23994)	Patient must have demonstrated an adequate response to treatment with this drug at least once in a lifetime, with an adequate response defined as a reduction in phenylalanine levels from baseline during initial responsiveness testing of no less than 30%
23988	**Treatment criteria:**
11331	Must be treated by a metabolic physician; OR
23987	Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
	AND
	Treatment criteria:
NEW	Patient must not be undergoing treatment with this drug under this Treatment phase, following completion of this authority application, for more than 13 cumulative months (assuming 1 month consists of 30 days)
	AND
NEW	**Treatment criteria:** Patient must not be undergoing simultaneous treatment with this drug under another non-maternal PBS-listing (apply under either listing type, but not both simultaneously)
	Population criteria:
NEW	Patient must be actively trying to conceive
NEW	**Administrative advice:** Request an appropriate maximum quantity (with the number of packs being a whole number) to provide approximately 30 days treatment duration per dispensing, based on dosing no greater than 20 mg/kg per day.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
NEW	**Administrative advice:** This PBS listing intends to subsidise up to 13 cumulative months (assuming 1 month consists of 30 days) of treatment during the pre-conception phase per known pregnancy. The time taken to conceive can vary for each patient, but where this treatment phase of 'pre-conception through to when pregnancy becomes first known' exceeds a cumulative 13 months, continued treatment beyond this time up to the point of conception, is not PBS subsidised.

	13 cumulative months comprises of the time taken to achieve desired phenylalanine level control and the time taken for pregnancy to become known (e.g. If it takes 3 months to reach desired phenylalanine level control, 10 months of PBS-subsidised treatment remain in which to achieve pregnancy; if it takes only 1 month to reach desired phenylalanine level control, 12 months of PBS-subsidised treatment remain in which to achieve pregnancy)
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
7608	**Administrative Advice:** Special pricing arrangements apply
25796	**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.
NEW	**Indication:** Maternal hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
	Treatment Phase: Existing pregnancy to birth
	Population criteria:
NEW	Patient must be pregnant
	Clinical criteria:
NEW	Patient must have demonstrated an adequate response to treatment with this drug at least once in a lifetime, with an adequate response defined as a reduction in phenylalanine levels from baseline during initial responsiveness testing of no less than 30%
23988	**Treatment criteria:**
11331	Must be treated by a metabolic physician; OR
23987	Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician
	AND
	Treatment criteria:
NEW	Patient must not be undergoing further treatment with this drug as a PBS benefit, post-partum in the absence of actively trying to conceive a subsequent child/a known subsequent pregnancy
	AND
NEW	**Treatment criteria** Patient must not be undergoing simultaneous treatment with this drug under another non-maternal PBS-listing (apply under either listing type, but not both simultaneously)
NEW	**Administrative advice**: Request an appropriate maximum quantity (with the number of packs being a whole number) to provide approximately 30 days treatment duration per dispensing, based on dosing no greater than 20 mg/kg per day.
NEW	**Administrative advice:** Request an appropriate number of repeats (whole number) relative to the expected birth date such that treatment is not continued post-partum by a whole prescription quantity. If the expected birth date is within the next 30 days at the time of the authority application, do not request repeats.
NEW	**Administrative Advice:** This PBS listing intends to subsidise treatment only whilst the patient is pregnant. Treatment is to be discontinued upon birth under this listing. Whilst a patient may benefit from continued treatment post-partum, continued treatment with this drug post-partum is not PBS subsidised in the absence of actively trying to conceive again/a known subsequent pregnancy.

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

13 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.

14 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 for maternal women.