

5.23 SAPROPTERIN

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

1 Purpose of Application

1.1 The minor submission requested:

- the listing of a 100 mg and 500 mg powder for oral solution form of sapropterin for hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency and HPA due to phenylketonuria (PKU); and
- a change in authority level of the current listing for sapropterin for HPA due to BH4 from Authority Required (in writing) to Authority required (telephone).

2 Requested listing

2.1 The proposed listing of 100 mg and 500 mg powder for oral solution forms of sapropterin are for the same indications as the currently listed 100 mg soluble tablet form.

2.2 The proposed amendment to the authority level of sapropterin for HPA due to BH4 from Authority required (in writing) to Authority Required (telephone) is intended to align the authority level with the listing of sapropterin for HPA due to PKU.

2.3 While not part of the original submission, the pre-PBAC response requested the PBAC consider whether nurse practitioners could be included as a prescriber for sapropterin as continuing treatment for HPA due to BH4 deficiency to align the prescriber types for this indication with the listing of sapropterin for HPA due to PKU.

3 Background

3.1 Sapropterin 100 mg and 500 mg powder was TGA registered in December 2018 'for the treatment of HPA in sapropterin-responsive adult and paediatric patients with PKU or BH4 deficiency'. The TGA considered the powder to be bioequivalent to the tablet.

3.2 The recommended doses of sapropterin are the same for tablet and powder formulations:

- The starting dose of sapropterin in adult and paediatric patients with PKU is 10 mg/kg once daily. The dose is adjusted to achieve and maintain adequate blood phenylalanine levels. The recommended daily dose is between 5 and 20

mg/kg/day.

- The starting dose of sapropterin in adult and paediatric patients with BH4 deficiency is 2 to 5 mg/kg daily. The dose is adjusted to achieve and maintain adequate blood phenylalanine levels. The recommended total daily dose is between 2 and 20 mg/kg/day.

3.3 Sapropterin has been considered by the PBAC five times previously:

- November 2011: a major submission for sapropterin tablets was considered for both PKU and BH4 deficiency and was not recommended for PBS listing.
- July 2012: a resubmission was considered for BH4 deficiency, and was deferred.
- November 2012: a minor resubmission was considered for BH4 deficiency, and was recommended for listing as Authority Required (in writing) to reduce the risk of leakage to patients with PKU.
- March 2018: a major resubmission was considered for sapropterin tablets for HPA due to PKU, and was deferred.
- November 2018: a minor resubmission was considered for sapropterin for HPA due to PKU and recommended for listing. This extension to the indication was PBS-listed on 1 May 2019 as an Authority Required (telephone) listing.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical claim

4.3 The submission claimed that the powder formulation of sapropterin has improved palatability, a shorter reconstitution time, better solution clarity, and longer stability after being dissolved. Further, the 500 mg dosage strength was proposed to improve convenience and reduce the likelihood of incorrect dosing for patients taking larger doses.

4.4 The request to amend the current restriction level for sapropterin for BH4 was for consistency between indications, and to alleviate the administrative burden on prescribers. As the November 2012 PBAC recommendation for a written authority for HPA due to BH4 deficiency was intended to reduce the risk of leakage into patients with HPA due to PKU, the submission requested to revisit the restriction level given that both indications are were PBS listed at the time of the submission.

Pricing considerations

- 4.5 The proposed published and effective AEMP for sapropterin 100 mg powder is the same as for the 100 mg tablets. The proposed published and effective AEMP for sapropterin 500 mg powder was calculated using the corresponding AEMP per mg of sapropterin.
- 4.6 The submission requested the same Special Pricing Arrangement for the powder formulations as for the currently listed tablet, and requested that both new strengths be included under the current Risk Sharing Arrangements (RSAs).
- 4.7 Special Pricing Arrangements for sapropterin only apply for the HPA due to PKU indication.

Estimated PBS usage & financial implications

- 4.8 The requested listings of the 100 mg and 500 mg sapropterin powder are the same as the currently listed 100 mg soluble tablets, however, the maximum quantity for the 500 mg powder formulation is different to the 100 mg powder and tablet formulations as outlined in the table below.

Table 1: Total amount of sapropterin per maximum quantity supplied

	100 mg tablet/powder (mg)	500 mg powder
BH4 – initial and continuing	18,000	15,000
PKU – initial responsiveness testing	9,000	15,000
PKU – first and subsequent continuing	18,000	15,000

- 4.9 The submission considered that while listing a 100 mg powder would have no financial implication, the listing of a 500 mg powder may result in a slight increase in prescription numbers due to the differences in maximum quantity. However, the submission proposed that the powder formulations be included under the existing RSAs.
- 4.10 The PBAC noted that sapropterin is currently subject to separate RSAs encompassing subsidisation caps for each indication (HPA due to BH4 deficiency and HPA due to PKU).

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the listing of a 100 mg and a 500 mg powder for oral solution form of sapropterin for hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency and HPA due to phenylketonuria (PKU) at a price per mg equivalent to the currently listed 100 mg tablet formulation. The PBAC also recommended the

Public Summary Document – July 2019 PBAC Meeting

change in authority level of the current listing for sapropterin for HPA due to BH4 deficiency from Authority Required (in writing) to Authority Required (telephone).

- 5.2 In making this recommendation, the PBAC noted that the powder formulation was bioequivalent to the existing tablet formulation.
- 5.3 The PBAC recalled that a written authority was originally recommended for the listing of sapropterin for HPA due to BH4 deficiency to manage the risk of leakage into patients with HPA due to PKU. The PBAC considered that the change in authority level for the HPA due to BH4 deficiency listing was considered appropriate now that sapropterin is also PBS-listed for HPA due to PKU.
- 5.4 The PBAC considered that despite the differences in the maximum quantity of sapropterin supplied between the 500 mg powder and the existing 100 mg tablet, the financial impact would likely be minimal, and noted that the new formulations would be included under the same RSAs as the tablet.
- 5.5 The PBAC has previously considered that sapropterin is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners for the treatment of HPA due to PKU. The PBAC considered it was appropriate for the prescriber types to be aligned across the indications, and recommended that nurse practitioners should also be able to prescribe sapropterin for HPA due to BH4 deficiency as a continuing treatment.
- 5.6 The PBAC noted that its recommendation was for new forms of an already listed drug and advised that because the recommended listing was not expected to alter the efficacy or toxicity of the treatment, or address a high and urgent unmet clinical need, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 5.7 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg powder for oral liquid, 30 sachets	6	0	Kuvan	Pharmaceutical
500 mg powder for oral liquid, 30 sachets	1	0		Australia Pty Ltd

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
PBS Indication:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
Treatment phase:	Initial
Restriction Level:	<input checked="" type="checkbox"/> Authority Required –Telephone
Treatment criteria:	Must be treated by a metabolic physician.
Clinical criteria:	Patient must have hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency.
Prescriber instructions:	Patient must have documented tetrahydrobiopterin (BH4) deficiency using tests for BH4 loading and/or urine pterin metabolites, blood spot dihydropteridine reductase (DHPR) and have cerebrospinal fluid neurotransmitter metabolites measured.
Administrative Advice	<p>Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment with sapropterin to be assessed.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg powder for oral liquid, 30 sachets	6	5	Kuvan	Pharmaceutical
500 mg powder for oral liquid, 30 sachets	1	5		Australia Pty Ltd

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
PBS Indication:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
Treatment phase:	Continuing
Restriction Level:	<input checked="" type="checkbox"/> Authority Required –Telephone
Treatment criteria:	<p>Must be treated by a metabolic physician; OR</p> <p>Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician.</p>

Public Summary Document – July 2019 PBAC Meeting

Clinical criteria:	Patient must have hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency, AND Patient must have previously been issued with an authority prescription for this drug; OR Patient must have accessed non-PBS-subsidised treatment prior to 1 May 2014.
Prescriber instructions:	Patient must have documented tetrahydrobiopterin (BH4) deficiency using tests for BH4 loading and/or urine pterin metabolites, blood spot dihydropteridine reductase (DHPR) and have cerebrospinal fluid neurotransmitter metabolites measured.
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
SAPROPTERIN DIHYDROCHLORIDE			BioMarin
100 mg powder for oral liquid, 30 sachets	3	0	Kuvan Pharmaceutical Australia Pty Ltd
500 mg powder for oral liquid, 30 sachets	1	0	

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Initial treatment – responsiveness testing
Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	Must be treated by a metabolic physician.
Clinical criteria:	Patient must not have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have a baseline blood phenylalanine level above 360 µmol/L and be less than one month of age; OR Patient must have a baseline blood phenylalanine level above 600 µmol/L and be more than one month of age; AND The treatment must be for the purpose of initial responsiveness testing for a period of 24 hours in a patient less than one month of age; OR The treatment must be for the purpose of initial responsiveness testing for a period of 7 days in a patient aged more than one month.
Population criteria:	Patient must be under 18 years of age.
Prescriber instructions:	Dietary phenylalanine intake must be maintained at a constant levels. Patients or their parent/guardian should be assessed for their ability to comply with the sapropterin protocol and PKU diet prior to conducting initial responsiveness testing.
Administrative advice:	Special pricing arrangements apply Patients will be eligible for a maximum of one PBS subsidised prescription as initial therapy to enable their response to treatment with sapropterin to be assessed.

Public Summary Document – July 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg powder for oral liquid, 30 sachets	6	5	Kuvan	Pharmaceutical Australia Pty Ltd
500 mg powder for oral liquid, 30 sachets	1	5		

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	First continuing treatment
Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	Must be treated by a metabolic physician; OR Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment under the Initial - responsiveness testing restriction with this drug for this condition; AND Patient must have demonstrated a response to treatment with this drug of greater than or equal to a 30% reduction in phenylalanine levels from baseline during initial responsiveness testing.
Population criteria:	Patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition.
Prescriber instructions:	Blood phenylalanine levels must be based on measurements taken during stable periods of the condition. Dietary phenylalanine intake must be maintained at a constant level.
Administrative advice:	Special pricing arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg powder for oral liquid, 30 sachets	6	5	Kuvan	Pharmaceutical Australia Pty Ltd
500 mg powder for oral liquid, 30 sachets	1	5		

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Subsequent continuing
Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	Must be treated by a metabolic physician; OR Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction; OR Patient must have previously received PBS-subsidised treatment with this drug for this condition under the Grandfather treatment restriction; AND Patient must be undergoing regular phenylalanine testing and assessment of adherence to dietary modifications.
Population criteria:	Patient must have been under 18 years of age at the time treatment with this drug was initiated for this condition.

Public Summary Document – July 2019 PBAC Meeting

Administrative advice:	Special pricing arrangements apply.
-------------------------------	-------------------------------------

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg powder for oral liquid, 30 sachets	6	0	Kuvan	Pharmaceutical Australia Pty Ltd
500 mg powder for oral liquid, 30 sachets	1	0		

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
PBS Indication:	Hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU)
Treatment phase:	Grandfather treatment
Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	Must be treated by a metabolic physician; OR Must be treated by a nurse practitioner experienced in the treatment of phenylketonuria in consultation with a metabolic physician.
Clinical criteria:	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to 1 May 2019, AND Patient must have demonstrated a response to treatment with this drug of greater than or equal to 30% reduction in phenylalanine levels from baseline during initial responsiveness testing, AND Patient must have a documented diagnosis of PKU.
Population criteria:	Blood phenylalanine levels must be based on measurements taken during stable periods of the condition. Dietary phenylalanine intake must be maintained at constant levels. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a grandfathered patient must qualify under the Subsequent continuing treatment criteria.
Administrative advice:	Special pricing arrangements apply.

6.2 Amend existing listing as follows:

Item number 10086W

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE				BioMarin
100 mg soluble tablet, 30	1	0	Kuvan	Pharmaceutical Australia Pty Ltd

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
PBS Indication:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
Treatment phase:	Initial

Public Summary Document – July 2019 PBAC Meeting

Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Written <input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	<i>Must be treated by a metabolic physician.</i>
Clinical criteria:	Patient must have hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency.
Prescriber instructions:	Patient must have documented tetrahydrobiopterin (BH4) deficiency using tests for BH4 loading and/or urine pterin metabolites, blood spot dihydropteridine reductase (DHPR) and have cerebrospinal fluid neurotransmitter metabolites measured. The authority application must be made in writing.
Administrative advice:	<p>Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment with sapropterin to be assessed.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004</p>

Item number 10087X

Name, Restriction, Manner of administration and form	Max. Qty	№ of Rpts	Proprietary Name and Manufacturer	
SAPROPTERIN DIHYDROCHLORIDE 100 mg soluble tablet, 30	1	0	Kuvan	BioMarin Pharmaceutical Australia Pty Ltd

Category / Program:	Section 85
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
Condition:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
PBS Indication:	Hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency
Treatment phase:	Continuing
Restriction Level:	<input checked="" type="checkbox"/> Authority Required – Written <input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	<i>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.</i>
Clinical criteria:	Patient must have hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency, AND Patient must have previously been issued with an authority prescription for this drug; OR Patient must have accessed non-PBS-subsidised treatment prior to 1 May 2014.

Public Summary Document – July 2019 PBAC Meeting

Prescriber instructions:	Patient must have documented tetrahydrobiopterin (BH4) deficiency using tests for BH4 loading and/or urine pterin metabolites, blood spot dihydropteridine reductase (DHPR) and have cerebrospinal fluid neurotransmitter metabolites measured. The authority application must be made in writing
Administrative advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004

7 Context for Decision

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

8 Sponsor's Comment

BioMarin would like to thank the PBAC for its consideration.