PUBLIC SUMMARY DOCUMENT
Product: Sapropterin dihydrochloride, soluble tablet, 100 mg (equivalent to 77 mg of sapropterin), Kuvan®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To seek a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the initial and continuing treatment of:
1) hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) in patients who are sapropterin responsive and are:
a) 10 years of age or younger
b) 11 to 17 years of age
c) 18 years of age or older who meet certain criteria.
2) HPA due to PKU or tetrahydrobiopterin (BH4) in pregnant women, who meet certain criteria and are sapropterin responsive
3) HPA due to BH4 deficiency in patients who are sapropterin responsive

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Sapropterin was granted orphan drug status and TGA registered on 21 October 2010 for the indication:

> For the treatment of hyperphenylalaninaemia (HPA) in sapropterin-responsive adult and paediatric patients, with phenylketonuria (PKU) or tetrahydrobiopterin (BH4) deficiency.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Authority Required
Treatment under the supervision of a paediatrician or metabolic clinician of patients 10 years of age or younger, diagnosed with hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) with a phenylalanine level > 350 μmol/L.

Patients will be eligible for a maximum of 1 script as initial therapy to enable their response to treatment to be assessed. If adequate response is not achieved within 1 month, the patient is no longer eligible for PBS-subsidised treatment with sapropterin.

Authority Required
Continuing PBS-subsidised treatment, in paediatric patients with hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU), who have a ≥ 30 percent reduction in blood phenylalanine levels.

Authority Required
Treatment under the supervision of a paediatrician or metabolic clinician of patients 11 to 17 years inclusive, diagnosed with hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) with a phenylalanine level > 400 μmol/L.

Patients will be eligible for a maximum of 1 script as initial therapy to enable their response to treatment to be assessed. If adequate response is not achieved within 1 month, the patient is no longer eligible for PBS-subsidised treatment with sapropterin.

Authority Required
Continuing PBS-subsidised treatment, in paediatric patients with hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) who have a ≥ 30 percent reduction in blood phenylalanine levels.

Authority Required
Treatment under the supervision of a metabolic clinician of patients 18 years of age or older, diagnosed with hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) with a phenylalanine level > 600 μmol/L.

Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment to be assessed. If adequate response is not achieved within one month, the patient is no longer eligible for PBS-subsidised treatment with sapropterin.

Authority Required
Continuing PBS-subsidised treatment, in adult patients with hyperphenylalaninaemia (HPA), due to phenylketonuria (PKU), who have a ≥30% reduction in blood phenylalanine levels.

Authority Required
Treatment under the supervision of a metabolic clinician of women, diagnosed with hyperphenylalaninaemia (HPA), due to phenylketonuria (PKU) or tetrahydrobiopterin (BH4), with phenylalanine level > 240 μmol/L, who are pregnant.

Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment to be assessed. If adequate response is not achieved within one month, the patient is no longer eligible for PBS-subsidised treatment with sapropterin.

Authority Required
Continuing PBS-subsidised treatment, in pregnant patients with hyperphenylalaninaemia (HPA), due to phenylketonuria (PKU) or tetrahydrobiopterin (BH4), who respond to treatment.

Authority Required
Treatment under the supervision of a paediatrician or metabolic clinician of patients diagnosed with hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency.

Patients will be eligible for a maximum of one script as initial therapy to enable their response to treatment to be assessed. If adequate response is not achieved within one month, the patient is no longer eligible for PBS-subsidised treatment with sapropterin.

Authority Required
Continuing PBS-subsidised treatment, in patients with hyperphenylalaninaemia (HPA) due to tetrahydrobiopterin (BH4) deficiency, who respond to treatment.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Hyperphenylalaninaemia (HPA) is a chronic abnormal elevation in blood levels of phenylalanine resulting from reduced activity of the liver enzyme phenylalanine hydroxylase (PAH). Phenylketonuria (PKU) and tetrahydrobiopterin (BH-4) deficiency account for the majority of cases of clinically significant HPA.

HPA is a rare, autosomal recessive condition which is detected through the Newborn Screening program. The estimated prevalence of HPA in Australia is approximately 2000 individuals. 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 phenylalanine diet achieved by controlled dietary restriction of whole protein, with concomitant administration of commercial phenylalanine-free protein supplements. The majority of Australian patients with HPA due to BH4 deficiency are treated with hospital-funded synthetic BH4.

The submission proposed that in the treatment of PKU, sapropterin would be an alternative therapy to current dietary management. In BH4 deficiency, sapropterin would be an alternative therapy to synthetic BH4.

6. Comparator

The submission nominated placebo (plus standard management: phenylalanine (Phe)-restricted diet with Phe-free protein supplements) as the comparator for sapropterin (added to standard management) in patients with BH4 responsive PKU.

The PBAC did not accept that this was the appropriate comparator, *see Recommendation and Reasons.*

The submission nominated prior treatment with sapropterin as the comparator for patients with BH4 deficiency.

The PBAC accepted that this was the appropriate comparator, *see Recommendation and Reasons.*

7. Clinical Trials

For BH4 responsive PKU, the basis of the submission was two randomised placebo controlled fixed dose trials (PKU-003, and PKU-006 Part 2), comparing treatment with sapropterin (in addition to a Phe-restricted diet) with placebo (dietary control of Phe alone), in known responders to sapropterin and tolerance to normal diet. Responders suitable for inclusion in these trials were identified in two single arm open-label lead-in phase 2 studies (PKU-001 and PKU-006 Part 1, respectively). Two extension studies (PKU-004 and PKU-008) examined dose response and safety as supporting studies.

For BH4 deficiency, the basis of the submission was one small single arm phase 2 open-label study (PKU-007) of patients switching from a non-registered formulation of BH4 to sapropterin or commencing treatment with sapropterin, while maintaining pre-trial Phe dietary management. The submission also presented one published open-label study (Kitagawa, 1990 (Japanese)), 11 published case series reports (Shintaku, 2009; Chien, 2001; Al Aqeel, 1991; Cabalska, 2002; Kao, 2004; Wang, 2006; Ye, 2002; Ye, 2007; Jaggi, 2008; Lee, 2006 and Liu, 2008) and one post marketing report (2004) as supporting studies.

Details of the trials published at the time of submission are in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
PKU randomised controlled trials		
PKU-003 Levy et al.	Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study.	*Lancet* 2007; 370:504-510.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
PKU-006 Trefz et al.	Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomised double-blind, placebo-controlled study.	*Journal of Pediatrics* 2009; 154:700-707.
PKU open-label studies		
PKU-001 Burton et al. 2007.	The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-Tetrahydrobiopterin): a phase II, multicentre, open-label, screening study.	*Journal of Inherited Metabolic Diseases 2007;* 30:700-707.
PKU-004 Lee et al.	Safety and efficacy of 22 weeks of treatment with Sapropterin dihydrochloride in patients with phenylketonuria.	*American Journal of Medical Genetics Part A* 2008; 146A:2851-2859.
BH4 deficiency other published studies		
Al Aqeel 1991	Biopterin-dependent hyperphenylalaninaemia due to deficiency of 6-pyruvoyl tetrahydropterin synthase,	*Neurology* 1991; 41:730-737.
Cabalska 2002	[Atypical phenylketonuria treatment effectiveness.] [Polish]	*Med Wieku Rozwoj* 2002; 6:193-202.
Chien 2009	Treatment and outcome of Taiwanese patients with 6-pyruvoyltetrahydropterin synthase gene mutations.	*Journal of Inherited Metabolic Diseases* 2009; 24:815-823.
Jaggi 2008	Outcome and long-term follow-up of 36 patients with tetrahydrobiopterin deficiency.	*Molecular Genetics and Metabolism* 2008; 93:295-305.
Kao 2004	Subtle brain dysfunction in treated 6-pyruvoyl-tetrahydropterin synthase deficiency: relationship to motor tasks and neurophysiological tests.	*Brain and Development* 2004; 26:93-98.
Kitagawa 1990	Clinical results of using apropterin hydrochloride (R-tetrahydrobiopterin) for atypical hyperphenylalaninaemia.	*Japanese Journal of Pediatric Medicine* 1990; 22:1737-1750.
Lee 2006	Long-term follow-up of Chinese patients who received delayed treatment for 6-pyruvoyl-tetrahydropterin synthase deficiency.	*Molecular Genetics and Metabolism* 2006; 86:128-134.
Liu 2008	Long-term follow-up of Taiwanese Chinese patients treated early for 6-pyruvoyltetrahydropterin synthase deficiency.	*Archives of Neurology* 2008; 65:387-392.
Shintaku 2009	Longitudinal follow-up of tetrahydrobiopterin (BH4) therapy in patients with BH4 deficiency in Japan.	*Molecular Genetics and Metabolism* 2009; 98:9 (abstract 128).
Wang 2006	[Study on tetrahydrobiopterin deficiency in Northern Chinese population.] [Chinese]	*Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2006; 23:275-279.
Ye 2002	Screening for tetrahydrobiopterin deficiency among hyperphenylalaninaemia patients in Southern China.	*Chinese Medical Journal* 2002; 115:217-221.
Ye 2007	[Diagnosis, treatment and long-term following up of 223 patients with hyperphenylalaninemia detected by neonatal screening programs.] [Chinese]	*Zhonghua Yu Fang Yi Xue Za Zhi* 2007; 41:189-192.

Abbreviations: BH4 = tetrahydrobiopterin.

8. Results of Trials

PKU: Lead-in studies PKU-001 and PKU-006 Part 1

The proportion of responders to sapropterin on day 8 of treatment, from Trial PKU-001 and PKU-006 part 1, are summarised in the table below by baseline blood Phe level subgroups.

Proportion of responders at 8 days of treatment (≥ 30% reduction in Phe)

Trial ID	Baseline Phe	Responders n	N	Proportion responders (95% CI)
PKU-001	<600µmol/L[a]	31	57	54% (41, 68)
	≥600µmol/L	65	428	15% (12, 19)
	All	96	485	20% (16, 23)
PKU-006 Part 1	All	50	90	56% (45, 66)

Abbreviations: PKU = phenylketonuria; Phe = phenylalanine.

[a] Entry criteria required a blood Phe level ≥450µmol/L.

In Trial PKU-001, the rate of response to sapropterin was higher in patients with low baseline blood Phe levels < 600 µmol/L (54%) compared to patients with blood Phe levels ≥ 600 µmol/L (15%). This was consistent with Trial PKU-006 Part 1, which reported a response rate of 56% for patients with blood Phe levels ≤ 480 µmol/L at baseline, i.e. the rate of response to sapropterin appears to be higher in patients controlled on a Phe-restricted diet compared to patients who are uncontrolled. Trial PKU-006 used a higher dose of sapropterin compared to Trial PKU-001 (20 mg/kg/day and 10 mg/kg/day respectively).

PKU: Reduction in blood Phe levels in Trial PKU-003, PKU-006 part 2 and PKU-004

In trial PKU-003, all participants who received at least one post baseline dose were included in the analysis. For subjects who were missing their Week 6 blood Phe measurement, the LOCF was used to impute complete data for the analysis. The analysis of the primary endpoint included approximately 98% of participants.

Trial PKU-003 reported that patients treated with sapropterin (10 mg/kg/day) and a Phe-restricted diet had a statistically significantly larger reduction in blood Phe levels over 6 weeks compared to patients on Phe-restricted diet alone, with a mean difference of -245 (95% CI: -350, -141; p < 0.001). Mean blood Phe levels fell to 606.9 µmol/L (± 377.0) in patients treated with sapropterin.

In Trial PKU-006 part 2, the mean change from baseline to endpoint was not the primary endpoint, as the overall objective was to determine patients' tolerance to Phe supplementation. Therefore, Phe levels beyond week 3 are not indicative of a reduction as a result of sapropterin treatment. The results for the mean change from baseline to 3 weeks in PKU-006 part 2 are summarised in the table below as after this time Phe supplementation commenced.

Mean change from baseline at 3 weeks in blood Phe in PKU-006 Part 2

Analysis	SAP		Pbo		Mean difference SAP - Pbo (95% CI)
	n	Mean (SD)	n	Mean (SD)	
Week 3	33	-148.5 (134.2)	12	-96.6 (243.6)	-51.9 (-197.1, 93.3)

Abbreviations: PKU = phenylketonuria; Phe = phenylalanine; SD = standard deviation.

Patients in Trial PKU-006 (20 mg/kg/day) achieved smaller reductions in blood Phe levels compared to patients in Trial PKU-003. Sample sizes were small and confidence intervals

for the placebo and sapropterin (phenoptin) treated patients were wide and overlapping suggesting high inter-patient variability. The reductions were not statistically significantly different from reductions achieved in patients on a Phe-restricted diet alone at 3 weeks.

The treatment effect reported in the fixed dose phase of PKU-004 (10 mg/kg/day) was reasonably constant from 12 to 22 weeks. Blood Phe levels measured at 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30 months of treatment and at termination in the long term safety study PKU-008 (3 years) were not presented, but the submission noted that blood Phe levels remained below 600 μmol/L in most patients achieving these levels in the placebo controlled trials, and were sustained within levels consistent with local clinical site recommendations for blood Phe control.

PKU: Tolerance of dietary Phe in Trial PKU-006 Part 2

Patients treated with sapropterin were able to tolerate statistically significantly larger amounts of dietary Phe (20.9 mg/kg/day) compared to patients on a Phe-restricted diet alone (2.9 mg/kg/day). There was considerable variability of Phe tolerance, and 14 of 33 patients treated with sapropterin required reductions in dietary Phe supplement due to blood Phe levels exceeding 360 μmol/L, at one or more visits.

While the data suggested that in some patients initially well controlled on Phe-restricted diets, the addition of sapropterin may increase tolerance of dietary Phe while maintaining blood Phe at ≤ 360 μmol/L; this was based on tolerance periods as short as 2 weeks.

BH4 deficiency: PKU-007

In Trial PKU-007 patients with abnormalities of BH4 biosynthesis maintained blood Phe levels of < 360 μmol/L at all time points. Patients with abnormalities of BH4 recycling showed mixed results, with only 1 of three patients maintaining blood Phe levels at < 360 μmol/L at the end of the study period. In the published case series and post marketing reports there appeared to be some evidence of patients with BH4 deficiency responding well to BH4 supplements, but it was unclear whether reductions in blood Phe observed in the studies resulted in a clinically important improvement in patient development and function, particularly in patients with recycling related BH4 deficiency.

For PBAC's comments on these results, see Recommendation and Reasons.

Patients treated with sapropterin most frequently reported pharyngolaryngeal pain, headache, vomiting, and abdominal pain. No seizures or neurological deficits were reported. More adverse events were reported in patients taking the higher dose of sapropterin in Trial PKU-006 (20 mg/kg/day) compared to the lower dose use in Trial PKU-003 (10 mg/kg/day).

Generally, the extended assessment of comparative harms was consistent with the safety profiles of the randomised controlled trials and extension studies.

9. Clinical Claim

The submission described sapropterin (plus standard management) as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo (plus standard management).

Based on trial PKU-003, the PBAC considered that although there were statistically significant larger reductions in mean blood Phe levels in patients treated with sapropterin compared to patients on a Phe-restricted diet alone after 6 week of treatment, blood Phe was not generally reduced to acceptable levels. It is uncertain if the blood Phe levels reported represent a clinically important difference in terms of irreversible or reversible neurological and behavioural sequelae or would be sustained over the long term.

The PBAC noted that overall, the extent of clinical benefit gained by adding sapropterin treatment to diet in a patient already controlled by diet is uncertain, and probably likely to be small.

10. Economic Analysis

The submission presented a cost utility analysis based on the randomised controlled trials.

Sapropterin treatment was compared to the Phe-free diet using three alternative levels of compliance to dietary restrictions and Phe-free protein supplements:

- 100% compliance (Phe-restricted diet);
- 50% compliance (relaxed diet/'real-life' scenario); and
- 0% compliance (uncontrolled)

The utility values used in the model were sourced from an independent study commissioned by the sponsor.

The submission used the relaxed diet as the comparator in the base case as this was considered to be reflective of 'real life' compliance with diet restrictions and supplements (based on selected case studies in the literature). The incremental cost per QALY gained was between $105,000 – $200,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS was estimated by the submission to be between $10 – $30 million in Year 5 including patients up to 40 years only and between $30 - $60 million in Year 5 including patients aged 40 and over.

12. Recommendation and Reasons

The PBAC noted the advice of the Highly Specialised Drugs Working Party, which supported listing sapropterin as a HSD under Section 100, and suggested consideration of listing adult treatment with sapropterin under Section 85.

The PBAC agreed that the appropriate comparator for patients with BH4 deficiency is prior treatment with sapropterin. However, the PBAC did not accept that placebo (plus standard management with a phenylalanine (Phe)-restricted diet in combination with Phe-free protein supplements) was the appropriate comparator for patients with HPA due to PKU. The PBAC considered the appropriate comparator for this patient population was standard management with a Phe-restricted diet in combination with Phe-free protein supplements as the same therapeutic outcome (reduction in blood Phe levels) is also achieved by adherence to a Phe-restricted diet in combination with Phe-free protein supplements. The PBAC considered it was likely that patients taking sapropterin would relax their dietary restrictions and in some

patients sapropterin would completely replace standard management.

The uncertainty around the comparator was compounded by inconsistency in the submission regarding use of sapropterin to replace or be used as an adjunct to diet. Although placebo as add-on to standard management including Phe-restricted diet and Phe-free protein supplements was nominated as the main clinical comparator, the economic model and utilities assumed sapropterin replaces a Phe-restricted diet with Phe-free protein supplements in all patients.

The PBAC noted the trend for a higher response rate to treatment with sapropterin in patients who had low baseline blood Phe levels, although it was acknowledged that this may be in part due to selection bias as those patients may be more motivated and compliant with a restrictive diet. There were no data to suggest whether treatment with sapropterin allows meaningful changes in dietary restrictions for some patients over the long term, or in patients uncontrolled using a Phe-restricted diet. The PBAC noted there was inconsistency between the clinical trials presented, which excluded pregnant women, children under the age of 4 years and patients with BH4 deficiency, and the proposed populations for whom listing was sought.

The PBAC was unclear whether the proposed restrictions for treatment of HPA with PKU, which are split by age group with different qualifying Phe levels, were clinically appropriate and how they would relate to clinical practice. The Committee also considered that the continuation rules would be impractical with patients swapping between the different age groups, the considerable variability in Phe levels, the uncertain clinical relevance of a 30% reduction in baseline levels and the lack of apparent treatment related variability in Phe levels. The PBAC noted the sponsor's suggestion in its Pre-Sub-Committee Response that it may be appropriate to limit reimbursement to patients less than 18 years of age. However, the TGA registered indication is for both adults and paediatric patients.

The PBAC noted the utility assigned to uncontrolled adults (0.20) was lower than that for uncontrolled children (0.37) and given the far more serious health implications in children considered this to be implausible. Uncertainty is also associated with the utilities derived for the health states included in the model given that the EQ-5D instrument was not developed for use in children, and the utilities derived describe the health of the parents of the children in several instances, rather than the health state of the children. Improvement in quality of life (QoL) for patients treated with sapropterin compared to diet alone appears to be attributable solely to relaxation of the diet. Given the uncertainty around the extent to which a relaxation of diet would be realised in clinical practice, the PBAC did not consider claiming this benefit in the model to be appropriate.

The PBAC considered that the utilisation estimate and the estimated financial implications associated with listing sapropterin were both uncertain and may be substantially underestimated. Both estimates inappropriately exclude patients over the age of 40 years and do not account for patients continuing PBS treatment with sapropterin via grandfathering which is inconsistent with the requested listing.

The PBAC noted there were inconsistencies identifying the appropriate age of the population for treatment with sapropterin between the proposed listing (all ages), the economic model (0-18 years) and the financial estimates (0-40 years). The PBAC also agreed with the issues

in relation to the economic modelling as identified by the ESC.

The PBAC considered that in the context of the uncertainties raised above, the base case (uncontrolled diet) incremental cost per QALY in the range of $75,000 – $105,000 was high and uncertain. Sensitivity analyses show that the model is sensitive to the age at which patients cease taking sapropterin and the utilities used in the model.

The PBAC therefore rejected the application to list sapropterin on the PBS because of uncertainty around the clinical place in therapy and high and uncertain cost effectiveness.

The PBAC acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

13. 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.

14. Sponsor's Comment

Merck Serono Australia is disappointed with the recommendation and will continue to work with the PBAC to ensure access to this valuable therapy for patients with this rare and serious condition.