PUBLIC SUMMARY DOCUMENT
Product: Sapropterin, soluble tablet, 100 mg (as dihydrochloride), Kuvan®
Sponsor: Merck Serono Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Re-submission requested a Section 100 (Highly Specialised Drugs Program) Private Hospital Authority Required and Public Hospital Authority Required (Streamlined) listing for treatment of hyperphenylalaninaemia (HPA) in patients demonstrated to have tetrahydrobiopterin (BH4) deficiency.

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.

If rejected, inclusion on the Life saving Drugs Program listing was requested.

Through the Life Saving Drugs Program (LSDP), the Australian Government provides subsidised access for eligible patients to expensive and potentially life saving drugs for very rare life threatening conditions.

Before a drug is made available on the LSDP it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

2. Background

At the November 2011 meeting, the PBAC rejected the submission for sapropterin because of uncertainty around the clinical place in therapy and high and uncertain cost effectiveness. The submission was for a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the initial and continuing treatment of:

1) HPA due to phenylketonuria (PKU) in patients who are sapropterin responsive and are: 10 years of age or younger, 11 - 17 years of age or 18 years of age or older who meet certain criteria;
2) HPA due to PKU or BH4 in pregnant women, who meet certain criteria and are sapropterin responsive; and
3) HPA due to BH4 deficiency in patients who are sapropterin responsive.

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 of hyperphenylalaninaemia (HPA) in a patient demonstrated to have tetrahydrobiopterin (BH4) deficiency.

Alternatively if rejected,

Inclusion under the Life Saving Drugs Program for BH4 deficiency was requested.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

BH4 deficiency is an inborn error of metabolism resulting from a lack of the essential enzyme co factor tetrahydrobiopterin. BH4 deficiency occurs in only 1-2 per 1,000,000 infants, making it extremely rare. It is estimated that less than 25 patients have BH4 deficiency in Australia. BH4 is an essential cofactor for the enzyme phenylalanine hydroxylase (PAH) which converts the amino acid phenylalanine (Phe) to tyrosine. BH4 deficiency prevents normal activity of PAH resulting in a toxic accumulation of Phe in the blood. This condition is referred to as HPA and is the hallmark of classic PKU as well as BH4 deficiency. In addition BH4 is also a cofactor for five enzymes involved in the biosynthesis of neurotransmitters dopamine, noradrenaline, adrenaline and serotonin and as such BH4 deficiency presents in almost all cases with neurological signs linked to impaired catecholamine and serotonin synthesis.

Typically, symptoms of BH4 deficiency appear a few months after birth and include poor sucking, impaired tone, microencephaly and a range of extrapyramidal signs. If left untreated profound neurological impairment, delayed psychomotor development and death in early childhood results. In Australia, BH4 deficiency is identified as part of the newborn screening program.

As the amount of BH4 entering the brain is insufficient to sustain appropriate synthesis of neurotransmitters, current clinical management includes synthetic BH4, a dopamine agonist (L-DOPA) in combination with carbidopa, 5-hydroxytryptophan (5-HTP) and in certain cases, folinic acid or a monoamine oxidase inhibitor.

The submission proposed that the place in therapy of sapropterin would be an alternative therapy to synthetic BH4 to reduce and normalise plasma phenylalanine levels independently of a low phenylalanine diet.

6. Comparator

The submission nominated no treatment with sapropterin as the comparator in the treatment of HPA in patients demonstrated to have BH4 deficiency. Since most patients in Australia are currently treated with synthetic BH4 through arrangements at individual public hospitals the submission also provided a comparison with prior treatment with other synthetic BH4 for patients with BH4 deficiency. Synthetic BH4 is only available in Australia through hospitals.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The following published trials and associated reports were presented in the submission:

Trial ID/First Author	Protocol title/ Publication title	Publication citation
BH4 deficiency published studies		
Curtius et al.	Atypical phenylketonuria due to tetrahydrobiopterin deficiency. Diagnosis and treatment with tetrahydrobiopterin, dihydrobiopterin and sepiapterin.	*Clinica Chimica Acta*, (1979), 93:2; 251-262
Danks et al.	Malignant hyperphenylalaninemia. Clinical features, biochemical findings, and experience with administration of biopterins.	*Pediatric Research*, (1979), 13:10; 1150-1155
Curtius et al.	In vivo studies of the tryptophan-5-hydroxylase system. Quantitation of serotonin and tryptamine using gas chromatography-mass fragmentography.	*Journal of Chromatography* (1980), 199: 171-179
Curtius et al.	Serotonin and dopamine synthesis in phenylketonuria.	*Advances in experimental medicine and biology* (1981), 133: 277-291
Niederwieser et al.	Atypical phenylketonuria with defective biopterin metabolism. Monotherapy with tetrahydrobiopterin or sepiapterin, screening and study of biosynthesis in man.	*European Journal of Pediatrics* (1982), 138:2; 110-112
Beck et al.	Diagnostic and therapeutic aspects of dihydrobiopterin deficiency. (ABSTRACT)	*Acta Paediatrica Scandinavica* (1983), 72:3; 449-454
Hsiao et al.	Atypical phenylketonuria with mild mental retardation caused by tetrahydrobiopterin deficiency in a Chinese family.	*Journal of Inherited Metabolic Disease* (1986), 9:2; 240-243
Niederwieser et al.	Peripheral tetrahydrobiopterin deficiency with hyperphenylalaninaemia due to incomplete 6-pyruvoyl tetrahydropterin synthase deficiency or heterozygosity.	*European Journal of Pediatrics* (1987), 146:3; 228-232
Meyer et al.	Deficit of tetrahydrobiopterin deficiency: A metabolic emergency. (ABSTRACT)	*Journal de Genetique Humaine (*1989), 37:4-5; 315-319
Tanaka et al.	On-off phenomenon in a child with tetrahydrobiopterin deficiency due to 6-pyruvoyl tetrahydropterin synthase deficiency (BH4 deficiency).	*European Journal of Pediatrics* (1989), 148:5; 450-452
Kitagawa et al.	Clinical results of using Sapropterin hydrochloride (R-tetrahydrobiopterin) for atypical hyperphenylalaninemia.	*Jpn J Pediatr Med* (1990), 22:11; 1737-1750
Al Aqeel et al.	Biopterin-dependent hyperphenylalaninaemia due to deficiency of 6-pyruvoyl tetrahydropterin synthase. (ABSTRACT)	*Neurology* (1991), 41; 730-737
Al Aqeel et al.	Response of 6-Pyruvoyltetrahydropterin Synthase Deficiency to BH4.	*J Child Neurol* (1992), 7; S26-S30

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Ponzone et al.	Catalytic activity of tetrahydrobiopterin in dihydropteridine reductase deficiency and indications for treatment.	*Pediatric Research* (1993), 33:2; 125-128
Ye et al.	Screening for 6-pyruvoyl-tetrahydrobiopterin synthase (PTPS) deficiency: clinical analysis of 9 patients with PTPS deficiency. (ABSTRACT)	*Zhonghua yi xue za zhi*, (2000), 80:7; 513-515
Chien et al.	Treatment and outcome of Taiwanese patients with 6-pyruvoyltetrahydropterin synthase gene mutations.	*J Inherit Metab Dis*. (2001), 24: 815-823
Dudešek et al.	Molecular analysis and long-term follow-up of patients with different forms of 6-pyruvoyl-tetrahydropterin synthase deficiency.	*European Journal of Pediatrics* (2001), 160:5; 267-276
Giewska et al.	The course of a pregnancy and 6 month observation of offspring from mother with late diagnosis of 6-pyruvoyl tetrahydrobiopterin synthase deficiency. (ABSTRACT)	*J Inherit Metab Dis* (2001), 24:Suppl 1 (31).
Cabalska et al.	Atypical phenylketonuria treatment effectiveness. [Polish] (ABSTRACT)	*Med Wieku Rozwoj* (2002), 6: 193-202
Kao et al.	Subtle brain dysfunction in treated 6-pyruvoyl-tetrahydropterin synthase deficiency: relationship to motor tasks and neurophysiological tests.	*Brain and Development* (2004), 26: 93-98
Demos et al.	6-Pyruvoyl-tetrahydropterin synthase deficiency with mild hyperphenylalaninaemia.	*Annals of Neurology* (2005), 58:1; 164-167
Gilles et al.	Hyperphenylalaninemia with a peripheral deficiency of the synthesis or tetrahydrobiopterin: Therapeutic approach. (ABSTRACT)	*Journal de Pharmacie Clinique* (2006), 25:3; 185-189
Lee et al.	Long-term follow-up of Chinese patients who received delayed treatment for 6-pyruvoyl-tetrahydropterin synthase deficiency.	*Molecular Genetics and Metabolism* (2006), 87:2; 128-134
Roze et al.	Long-term follow-up and adult outcome of 6-pyruvoyl-tetrahydropterin synthase deficiency.	*Movement Disorders* (2006), 21:2; 263-266
Wang et al. (2006a)	Long-term outcome and neuroradiological findings of 31 patients with 6-pyruvoyltetrahydropterin synthase deficiency.	*Journal of Inherited Metabolic Disease* (2006), 29:1; 127-134
Wang et al. (2006b)	Study on tetrahydrobiopterin deficiency in Northern Chinese population. Same population as Wang (2006a)(ABSTRACT)	*Chinese Journal of Medical Genetics* (2006), 23:3; 275-279
Tanaka et al.	Early initiation of L-DOPA therapy enables stable development of executive function in tetrahydrobiopterin (BH4) deficiency.	*Developmental Medicine and Child Neurology* (2007), 49:5; 372-376

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Ye et al.	Diagnosis, treatment and long-term following up of 223 patients with hyperphenylalaninemia detected by neonatal screening programs.[Chinese] (ABSTRACT)	*Zhonghua Yu Fang Yi Xue Za Zhi* (2007), 41: 189-192
Horvath et al.	Autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia: Evidence of a phenotypic continuum between dominant and recessive forms.	*Molecular Genetics and Metabolism* (2008), 94:1; 127-131
Jäggi et al.	Outcome and long-term follow-up of 36 patients with tetrahydrobiopterin deficiency.	*Molecular Genetics and Metabolism* (2008), 93:3; 295-305
Liu et al.	Long-term follow-up of Taiwanese Chinese patients treated early for 6-pyruvoyl-tetrahydropterin synthase deficiency.	*Archives of Neurology* (2008), 65:3; 387-392
Ogawa et al.	A case of 6-pyruvoyl-tetrahydropterin synthase deficiency demonstrates a more significant correlation of L-DOPA dosage with serum prolactin levels than CSF homovanillic acid levels.	*Brain and Development* (2008), 30:1; 82-85
Chien et al.	Treatment and outcome of Taiwanese patients with 6-pyruvoyltetrahydropterin synthase gene mutations.	*Journal of Inherited Metabolic Diseases* (2009), 24:815-823
Giovannini et al.	Severe PTPS deficiency in an adult lawyer with normal IQ. (ABSTRACT)	*Pteridines* (2009), 20:3; 104
Ngu et al.	6-pyruvoyl tetrahydropterin synthase deficiency-clinical and molecular profiles of six Malaysian patients. (ABSTRACT)	*Pteridines* (2009), 20:3; 105
Shintaku et al.	Longitudinal follow-up of tetrahydrobiopterin (BH4) therapy in patients with BH4 deficiency in Japan. (ABSTRACT)	*Molecular Genetics and Metabolism* (2009), 98:1-2; 9
Vatanavicharn et al.	Novel mutation affecting the pterin-binding site of PTS gene and review of PTS mutations in Thai patients with 6-pyruvoyltetrahydropterin synthase deficiency. Article in Press	*Journal of Inherited Metabolic Disease* (2009) 1-4
Leuzzi et al.	Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency.	*Clinical Genetics* (2010), 77:3; 249-257
Shintaku et al.	Long-term follow-up of tetrahydrobiopterin (BH4) therapy in patients with BH4 deficiency in Japan. (ABSTRACT)	*Journal of Inherited Metabolic Disease* (2010), 33:1; S101
Coughlin et al.	Dihydropteridine reductase deficiency and treatment with tetrahydrobiopterin: A case report. (ABSTRACT)	*Molecular Genetics and Metabolism* (2011), 102:3; 275
Croonen et al.	Phenylketonuria (PKU): Not always 'PKU'. (ABSTRACT)	*Tijdschrift voor Kindergeneeskunde* (2011), 78:5; 183-186

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Reviews of BH4 deficiency and its treatment (published in the last decade)		
Shintaku H	Disorders of tetrahydrobiopterin metabolism and their treatment.	*Current Drug Metabolism* (2002), 3:2; 123-131
Blau et al.	Disorders of phenylalanine and tetrahydrobiopterin metabolism.	in *Physician's Guide to the Treatment and Follow-up of Metabolic Diseases*: Heidelberger, Springer, (2002): 25-34
Ponzone et al.	Dihydropteridine Reductase Deficiency in Man: From Biology to Treatment.	*Medicinal Research Reviews* (2004), 24:2; 127-150
Longo N	Disorders of biopterin metabolism.	*Journal of Inherited Metabolic Disease* (2009), 32:3; 333-342
Bramwell B	Folinic acid, L-DOPA and 5-hydroxytryptophan in tetrahydrobiopterin deficiency: Treatment plan for a pediatric patient.	*International Journal of Pharmaceutical Compounding* (2011), 15:4; 316-319
Lagler et al.	The Kuvan. Adult maternal paediatric European registry (KAMPER): Patient characteristics. (ABSTRACT)	*Journal of Inherited Metabolic Disease* (2011), 34: S108

The submission acknowledged the ultra-rare nature of BH4 deficiency and the severe, irreversible sequelae that result from inadequate or untimely treatment make the conduct of randomised controlled trials unethical and unlikely. The clinical evidence relied on by the submission consisted of primarily case studies, from a wide time frame (1979-2011).

8. Results of Trials

The published citations generally showed that prompt effective treatment with synthetic BH4 in combination with neurotransmitter precursors (as required) is necessary for normal physical, intellectual and psychomotor development and survival beyond infancy in paediatric patients with BH4 deficiency.

Few adult patients were reported in the published citations and patients over the age of 30 years were rare. Only 10 paediatric and 3 adult patients (one treated with sapropterin) were identified in a survey of Australian special clinicians currently treating BH4 deficiency. The PBAC considered that the benefit of treatment with sapropterin for adult and elderly patients is uncertain, and some of these patients may derive equal benefit in terms of function and survival from a Phe restricted diet or in rare cases, no treatment at all.

The most commonly reported adverse events associated with sapropterin use were headache, upper respiratory tract infections, pharyngeal pain, cough, diarrhoea and vomiting. These events were transient and mild. Two adverse events (severe dystonia and nasopharyngitis), were reported as severe, but were transient and considered unrelated to sapropterin use.

The submission provided a Periodic Safety Update Report (PSUR) for sapropterin for the

period 2 June 2010 to 1 December 2010, previously provided in the November 2011 submission. The sponsor acknowledged that seizures/convulsions in addition to changes of behaviour (including aggression and irritability), allergic reactions, infections and insomnia continue to be closely monitored. Generally, the extended assessment of comparative harms was consistent with the safety profiles of the randomised controlled trials and extension studies in PKU and BH4 deficiency.

9. Clinical Claim

The submission described sapropterin as more effective than placebo and at least as effective as other synthetic BH4 formulations in the long term treatment of BH4 deficiency.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission noted that the lack of randomised clinical trials in BH4 deficiency and the low level of evidence available prevented construction of an informative and robust economic model. The submission presented a simple indicative evaluation of the cost per life year gained based on the requested price of sapropterin assuming all eligible patients will be treated from infancy to end of life at 81 years of age and 100% compliance.

The submission claimed that sapropterin was not cost effective and imposed an unreasonable economic burden on the patient or his/her guardian.

The estimated cost per life year gained is between $45,000 and $75,000 based on assumptions that patients are treated from infancy to 81 years of age and the base case cost/patient/year of sapropterin was between $45,000 and $75,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recalled that in November 2011, it had previously agreed that the appropriate comparator for patients with BH4 deficiency is prior treatment with sapropterin.

The PBAC noted that BH4 deficiency is an ultra-rare form of HPA, which can be diagnosed and differentiated from phenylketonuria with reasonable precision by the BH4 loading test and/or by genotype via a regimen of serum, cerebrospinal fluid (CSF) and urinary biomarkers (serum Phe, serum DHPR, CSF HVA, CSF 5-HIAA, urine biopterin and urine neopterin).

The PBAC further noted that treatment with a phenylalanine (Phe) restricted diet in BH4 deficient patients, in the majority of cases, is ineffective to prevent the progression of disability and mortality particularly in early infancy.

The PBAC accepted that the available clinical evidence for sapropterin is limited and of low quality. However, the PBAC considered that when it is evaluated in the context of a rare disease, where patients have been treated with BH4 replacement therapy for a number of

years, it is reasonable to conclude that appropriate treatment with synthetic BH4 (sapropterin), perhaps in combination with neurotransmitter precursors (L-DOPA or 5-HT), may lead to normal physical, intellectual and psychomotor development and life extension beyond infancy in paediatric patients with BH4 deficiency.

The PBAC considered that due to the extremely limited data available in adult patients, the benefit of treatment with sapropterin for adult and elderly patients is uncertain, and some of these patients may derive equal benefit in terms of function and survival from a Phe restricted diet or in rare cases, no treatment at all.

An updated survey of Australian specialised clinicians currently treating BH4 deficiency was presented in the submission.

Based on the clinicians survey of identified BH4 deficiency patients in Australia and the low prevalence of BH4 deficiency (BH4 deficiency is routinely screened for in newborns in Australia detecting 1-2 cases per million infants i.e. one case every 2-4 years), the PBAC considered that the submission's estimate maybe an overestimate.

The PBAC noted that the estimated cost per life year gained is between $45,000 and $75,000 based on assumptions that patients are treated from infancy to 81 years of age and the base case cost/patient/year of sapropterin was between $45,000 and $75,000.

The PBAC considered that the costs and utilisation of sapropterin presented in the submission are uncertain. Particularly as these factors will be predominantly influenced by paediatric requirements over the first 5 years of listing whereas the estimates in the submission assume a uniform distribution of patients over all ages (0-81 years), and are therefore primarily influenced by adult requirements.

The PBAC noted that due to the high cost of sapropterin it would not be considered cost effective for listing on the PBS and hence proceeded to consider the possible inclusion of sapropterin on the LSDP.

The PBAC was satisfied that the submission appropriately addresses and fulfils criteria 1 through 8 of the LSDP criteria. The PBAC noted that risk share agreements are a requirement of listing through the LSDP.

In regard to LSDP criteria B1, the PBAC was concerned that the proposed price of the drug was higher when compared with the effective price of the drug in some comparable overseas markets. The PBAC particularly noted the lower price available online from Canada.

The PBAC also requested that the sponsor provide information regarding the appropriateness of the 100 mg soluble tablet particularly for paediatric patients and clarify whether there is the possibility of wastage. The PBAC was also interested in stability data for the solution formed by dissolving the tablet, particularly as in reality, the patient could retain any remaining solution for the next dose.

The PBAC therefore deferred the submission so that discussion could take place with the sponsor regarding price, noting that further information regarding dissolution stability data and wastage could inform this discussion.

Recommendation:
Defer

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 – July 2012

Merck Serono is pleased to continue working with the PBAC and the Department to ensure timely access to Kuvan, through the LSDP, for patients with this rare and serious condition.

ADDENDUM

PUBLIC SUMMARY DOCUMENT
Product: Sapropterin, soluble tablet, 100 mg (as dihydrochloride), Kuvan®
Sponsor: Merck Serono Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The minor submission sought inclusion on the Life Saving Drugs Program (LSDP) for the treatment of hyperphenylalaninaemia (HPA) in patients demonstrated to have tetrahydrobiopterin (BH4) deficiency following a deferral at the July 2012 PBAC meeting.

Life Saving Drugs Program:
Through the LSDP, the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions.

Before a drug is made available on the LSDP it must generally be accepted by the Pharmaceutical Benefits Advisory Committee as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefits Scheme due to unacceptable cost-effectiveness.

2. Background

At the November 2011 meeting, the PBAC rejected a submission for sapropterin because of uncertainty around the clinical place in therapy and high and uncertain cost effectiveness. The submission was for a Section 100 (Highly Specialised Drugs Program (HSDP)) Authority required listing for the initial and continuing treatment of HPA due to phenylketonuria or BH4 deficiency in various patient groups.

A copy of the Public Summary Document (PSD) from the November 2011 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-sapropterin-nov11

At the July 2012 meeting, the PBAC deferred making a recommendation on a submission to list sapropterin as a Section 100 (HSDP) Authority required benefit for the treatment of HPA in patients demonstrated to have BH4 deficiency so that discussion could take place with the sponsor regarding price, noting that further information regarding dissolution stability data and wastage could inform this discussion.

3. Listing Requested and PBAC's View

The submission requested inclusion under the Life Saving Drugs Program for BH4 deficiency. The PBS restriction is yet to be finalised.

4. Summary of Submission

The submission proposed that the place in therapy of sapropterin would be an alternative therapy to synthetic BH4 to reduce and normalise plasma phenylalanine levels independently of a low phenylalanine diet.

The submission did not propose any change to the comparator of placebo as previously nominated in the deferred submission from July 2012.

No new clinical trial data were identified in the submission.

No new clinical claims were made in the submission.

No new economic evaluation was provided in the submission.

5. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

6. Recommendation and Reasons

The PBAC noted that sapropterin was originally submitted for Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of HPA in a patient demonstrated to have BH4 deficiency, and if rejected on cost-effectiveness grounds, LSDP listing for BH4 deficiency was requested.

The PBAC recalled that in July 2012, the submission was deferred to seek further information from the sponsor regarding the stability of sapropterin dissolved in water to form a solution, to address issues relating to wastage. The PBAC also sought further information regarding price, noting that the price proposed by the sponsor in July was considered higher than in other countries in cost relative terms.

On the matter of stability in solution, the PBAC noted that data provided by the sponsor indicates that all product specifications were not met when sapropterin tablets remained in solution for a period of time greater than 45 minutes. On this basis, sapropterin solution should be consumed immediately and cannot be stored until the next dose.

The PBAC noted the sponsor's claim that resulting wastage had been taken into account in previous submissions when the price of sapropterin was originally proposed. The PBAC also

noted that the sponsor has reduced the price of sapropterin making it comparable to other international prices including the price in Canada and the UK.

The PBAC noted that in BH4 deficiency, the starting dose in adult and paediatric patients is 2 to 5 mg/kg body weight once daily. Once adjusted to achieve and maintain adequate blood phenylalanine levels, the recommended daily dose is between 2 and 20 mg/kg/day.

The PBAC noted that the cost of listing sapropterin for eligible patients with BH4 deficiency would be less than $10 million per year.

The PBAC noted the difficulty of precisely calculating the cost effectiveness of sapropterin in BH4 deficiency. The PBAC recalled that in its July 2012 consideration, the cost of sapropterin was calculated to be between $45,000 and $75,000 cost per life year gained (LYG). With the price reduction offered in the current submission, this amount would be reduced but would remain within the range of between $45,000 and $75,000 cost per LYG.

The PBAC noted that in the previous submission no request had been made by the sponsor for consideration under the Rule of Rescue.

The four factors of the Rule of Rescue are as follows:

1. No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients.

The PBAC considered that no alternative non-pharmacological or pharmacological intervention exists for the treatment of BH4 deficiency.

2. The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.

The PBAC considered that BH4 deficiency is severe, progressive and expected to lead to premature death, particularly in paediatric patients. The PBAC particularly noted the severely limited life expectancy for infants diagnosed with BH4 deficiency.

3. The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.

The PBAC noted the sponsor's estimate of patient numbers and agreed that the patient population with definitive BH4 deficiency was extremely small.

4. The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC.

The PBAC considered that sapropterin does provide a significant clinical benefit and improvement to patients, commensurate with a rescue in these specific circumstances.

The PBAC therefore concluded that sapropterin for BH4 deficiency does meet the Rule of Rescue for listing on the PBS.

The PBAC considered that the risk of leakage into patients with phenylketonuria (PKU) was considerable. The PBAC recalled that it previously rejected a submission from the sponsor to list sapropterin under Section 100 (Highly Specialised Drug Program) for hyperphenylalaninaemia (HPA) in patients with PKU, on the basis of high and uncertain cost effectiveness.

The PBAC recommended listing sapropterin 100 mg soluble tablet on the PBS as a Section 85 Authority Required listing for BH4 deficiency under the Rule of Rescue. The PBAC also recommended that Authority applications should be in writing to the Complex Drugs and Programs unit of the Department of Human Services (formerly Medicare Australia), to further reduce the risk of leakage. The restriction will be finalised at a later date.

The PBAC recommended that the Safety Net 20 Day Rule should apply.

The PBAC recommended that sapropterin is not suitable for prescribing by nurse practitioners.

The PBAC requested that the Department review this listing in five years to confirm the number of continuing patients.

Recommendation:
SAPROPTERIN, soluble tablet, 100 mg (as dihydrochloride)

Restriction:	Authority Required To be finalised
Max Qty:	180
Rpts:	5

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 – November 2012

The sponsor did not provided further comment.