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

<u>Section 100 (Highly Specialised Drugs Program)</u>

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	Protocol title/ Publication title	Publication citation
BH4 deficiency published studies		
Curtius (1979)	Curtius H.C. 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 (1979)	Danks D.M. et al. Malignant hyperphenylalaninemia. Clinical features, biochemical findings, and experience with administration of biopterins.	Pediatric Research, 1979, 13:10 (1150-1155).
Curtius (1980)	Curtius H.C. 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 (1981)	Curtius H.C. et al. Serotonin and dopamine synthesis in phenylketonuria.	Advances in experimental medicine and biology, 1981, 133 (277-291).
Niederwieser (1982)	Niederwieser A. 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 (1983)	Beck B. et al. Diagnostic and therapeutic aspects of dihydrobiopterin deficiency. (ABSTRACT)	Acta Paediatrica Scandinavica, 1983, 72:3 (449-454).
Hsiao (1986)	Hsiao K.-J. et al. Atypical phenylketonuria with mild mental retardation caused by tetrahydrobiopterin deficiency in a Chinese family.	Journal of Inherited Metabolic Disease, 1986, 9:Suppl 2 (240-243).
Niederwieser (1987)	Niederwieser A. 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 (1989)	Meyer M. et al. Deficit of tetrahydrobiopterin deficiency: A metabolic emergency. (ABSTRACT)	Journal de Genetique Humaine, 1989, 37:4-5 (315-319).
Tanaka (1989)	Tanaka Y. 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 (1990)	Kitagawa T et al. Clinical results of using Sapropterin hydrochloride (R-tetrahydrobiopterin) for atypical hyperphenylalaninemia.	Jpn J Pediatr Med, 1990, 22:11 (1737-1750).
Al Aqeel (1991)	Al Aqeel et al. Biopterin-dependent hyperphenylalaninaemia due to deficiency of 6-pyruvoyl tetrahydropterin synthase. (ABSTRACT)	Neurology, 1991, 41 (730-737).
Al Aqeel (1992)	Al Aqeel A et al. Response of 6-Pyruvoyltetrahydropterin Synthase Deficiency to BH4.	J Child Neurol, 1992, 7 (S26-S30).
Ponzone (1993)	Ponzone A. et al. Catalytic activity of tetrahydrobiopterin in dihydropteridine reductase deficiency and indications for treatment.	Pediatric Research, 1993, 33:2 (125-128).
Ye (2000)	Ye J. 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).

Trial ID	Protocol title/ Publication title	Publication citation
Chien (2001)	Chien YH et al. Treatment and outcome of Taiwanese patients with 6-pyruvoyltetrahydropterin synthase gene mutations.	J Inherit Metab Dis., 2001, 24 (815-823).
Dudešek (2001)	Dudešek A. 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 (2001)	Giewska M, Bich W, Cyryowski. 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 (2002)	Cabalska et al. [Atypical phenylketonuria treatment effectiveness.] [Polish] (ABSTRACT)	Med Wieku Rozwoj, 2002, 6 (193-202).
Kao (2004)	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 (2005)	Demos M.K. et al. 6-Pyruvoyl-tetrahydropterin synthase deficiency with mild hyperphenylalaninaemia.	Annals of Neurology, 2005, 58:1 (164-167).
Gilles (2006)	Gilles C. 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 (2006)	Lee N.C. 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 (2006)	Roze E. et al. Long-term follow-up and adult outcome of 6-pyruvoyl-tetrahydropterin synthase deficiency.	Movement Disorders, 2006, 21:2 (263-266).
Wang (2006a)	Wang L. et al. 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 (2006b)	Wang L. et al. 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 (2007)	Tanaka Y. 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).
Ye (2007)	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 (2008)	Horvath G.A. 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 (2008)	Jäggi L. et al. Outcome and long-term follow-up of 36 patients with tetrahydrobiopterin deficiency.	Molecular Genetics and Metabolism, 2008, 93:3 (295-305).
Liu (2008)	Liu K.-M. 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 (2008)	Ogawa A. et al. A case of 6-pyruvoyl-tetrahydropterin synthase deficiency demonstrates a more significant correlation of L-DOPA dosage with	Brain and Development, 2008, 30:1 (82-85).

Trial ID	Protocol title/ Publication title	Publication citation
	serum prolactin levels than CSF homovanillic acid levels.	
Chien (2009)	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 (2009)	Giovannini M. et al. Severe PTPS deficiency in an adult lawyer with normal IQ. (ABSTRACT)	Pteridines, 2009, 20:3 (104).
Ngu (2009)	Ngu L.H. et al. 6-pyruvoyl tetrahydropterin synthase deficiency-clinical and molecular profiles of six Malaysian patients. (ABSTRACT)	Pteridines, 2009, 20:3 (105).
Shintaku (2009)	Shintaku H. 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 (2009)	Vatanavicharn N. 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 (2010)	Leuzzi V. et al. Phenotypic variability, neurological outcome and genetics background of 6-pyruvoyl-tetrahydropterin synthase deficiency.	Clinical Genetics, 2010, 77:3 (249-257).
Shintaku (2010)	Shintaku P. 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:Suppl 1 (S101).
Coughlin (2011)	Coughlin C.R. et al. Dihydropteridine reductase deficiency and treatment with tetrahydrobiopterin: A case report. (ABSTRACT)	Molecular Genetics and Metabolism, 2011, 102:3 (275).
Croonen (2011)	Croonen E.A. et al. Phenylketonuria (PKU): Not always 'PKU'. (ABSTRACT)	Tijdschrift voor Kindergeneeskunde, 2011, 78:5 (183-186).
Reviews of BH4 deficiency and its treatment (published in the last decade)		
Shintaku (2002)	Shintaku H. Disorders of tetrahydrobiopterin metabolism and their treatment.	Current Drug Metabolism, 2002, 3:2 (123-131).
Blau (2002)	Blau N and Burgard P 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 (2004)	Ponzone A. et al. Dihydropteridine Reductase Deficiency in Man: From Biology to Treatment.	Medicinal Research Reviews, 2004, 24:2 (127-150).
Longo (2009)	Longo N. Disorders of biopterin metabolism.	Journal of Inherited Metabolic Disease, 2009, 32:3 (333-342).
Bramwell (2011)	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 (2011)	Lagler M.F.B. et al. The Kuvan. Adult maternal paediatric European registry (KAMPER): Patient characteristics. (ABSTRACT)	Journal of Inherited Metabolic Disease, 2011, 34:Suppl 3 (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 (0-81years), 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

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.