Cost-effectiveness of sapropterin dihydrochloride (Kuvan®) for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment

The NCPE has issued a recommendation regarding the cost-effectiveness of sapropterin dihydrochloride (Kuvan®). Following NCPE assessment of the applicant's submission, sapropterin dihydrochloride (Kuvan®) is not considered cost-effective for the treatment of HPA in PKU and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (BioMarin Europe Limited) economic dossier on the cost effectiveness of sapropterin dihydrochloride**.** The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **September 2017**

Summary

In February 2017, BioMarin Europe Limited submitted a dossier examining the cost effectiveness of sapropterin dihydrochloride (Kuvan®) for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment.

The recommended daily dose of sapropterin dihydrochloride is calculated based on body weight (kilograms) which should be rounded to the nearest multiple of 100mg. The starting dose of sapropterin dihydrochloride is 10mg/kg/day in adult and paediatric patients with PKU. Doses may be adjusted between 5mg/kg/day up to 20 mg/kg/day to achieve and maintain adequate blood phenylalanine levels as defined by the physician. Sapropterin dihydrochloride is also licensed for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment. No submission for the BH4 deficient indication has been submitted to the NCPE, and therefore the NCPE cannot recommend reimbursement in this patient population.

In the submission, the primary comparator is a phenylalanine restricted diet. The principal analysis presented by the applicant is based on a subgroup of adult and paediatric patients with uncontrolled and partially controlled PKU who have been shown to be responsive to BH4 treatment.

1. Comparative effectiveness of sapropterin dihydrochloride

The applicant presented evidence in the form of one phase II study, four phase III studies, three phase IIIb studies, and 5 phase IV studies across a range of patient groups (paediatric population <4 years, maternal PKU, all ages PKU) and endpoints (reduction in phenylalanine levels, phenylalanine tolerance and neurological outcomes). The clinical development program for sapropterin dihydrochloride included two pivotal, randomised, placebo-controlled, phase III studies: PKU-003 and PKU-006 (Part 2) and the SPARK study.

The NCPE considers that the applicant has successfully demonstrated the short-term effects on reducing phenylalanine blood levels, whereby response is defined as ≥ 30% reduction of phenylalanine levels in a subset of BH4-responsive individuals. The strength of the evidence presented by the applicant is moderate for short-term effects on reducing blood phenylalanine levels ≥ 30% in a subset of initially BH4-responsive individuals, low for longer term effects phenylalanine blood level control whereby biochemical control is defined as a > 75% of phenylalanine levels in target range, low for increased phenylalanine tolerance, defined as an increase of 100% or more in natural protein and insufficient for all other long term clinically meaningful patient outcomes.

Given that blood phenylalanine is the primary marker for guiding treatment management plans in patients with PKU, and as sapropterin dihydrochloride has been shown to be effective in reducing blood phenylalanine levels ≥ 30% in the short term in a subset of initially BH4-responsive individuals, the NCPE acknowledges that it is plausible that sapropterin dihydrochloride could reduce the risk of long term effects on clinically meaningful outcomes in some patients. However, the NCPE also considered the scientific basis for this threshold of response which is consensus based and does not directly translate into a clinically meaningful outcome. A 30% reduction in phenylalanine levels does not always translate as a patient achieving optimal and safe target blood phenylalanine levels as defined by the European PKU guidelines 2017.

2. Safety of sapropterin dihydrochloride

No serious adverse events associated with sapropterin dihydrochloride were reported and no significant differences in adverse events relative to the placebo were noted in the PKU-003 six-week trial and the subsequent PKU-004 twenty two week open-label extension study presented by the applicant. The most commonly reported adverse effects, as per the SmPC are gastrointestinal (diarrhoea, vomiting, abdominal pain), neurological (dizziness, headache) and rhinorrhoea. Caution is advised when sapropterin dihydrochloride is utilised in patients with a pre-disposition to convulsions. Safety data on pregnant women who are treated pre-conception and during pregnancy, as well as data for their offspring was presented by the applicant from the PKUMOMS sub-registry. Severe adverse events identified by the investigators as possibly related to sapropterin dihydrochloride use were

premature labour (n= 1) and spontaneous abortion (n=1) and hypophagia for the offspring [premature birth (35weeks and 4 days), n=1]. One congenital malformation (cleft palate) of unknown aetiology was reported as unrelated to sapropterin dihydrochloride. Although there is limited information regarding the use of sapropterin dihydrochloride during pregnancy, the sub-registry data show that sapropterin dihydrochloride is generally well-tolerated.

3. Cost effectiveness of sapropterin dihydrochloride

The applicant submitted a decision analytic model which was constructed to assess the cost-utility of sapropterin dihydrochloride in combination with a phenylalanine restricted diet versus a phenylalanine restricted diet only in patients with PKU. The model developed by the applicant is a cohort based Markov-type model, which allows a hypothetical cohort of 1000 PKU patients to enter the model through the decision tree where they are assigned to either treatments. After a 4-week BH4 response test, sapropterin dihydrochloride responders' move on to the recursive Markov part of the model. The Markov model captures 5 health states defined as controlled, partially controlled, uncontrolled, asymptomatic and death; the absorbing state. A 1-year cycle length over a 100-year time horizon was assumed and a half cycle correction applied. The two key drivers of health outcome attainment in the economic model are transition probabilities between health states due to improved phenylalanine blood control, and increased phenylalanine tolerance.

Following a review of the cost utility model presented by the applicant, the NCPE concluded that it is not sufficiently robust, rendering it difficult to make any conclusions regarding the cost effectiveness of sapropterin dihydrochloride in the total PKU population or in any of the presented subgroups. The model structure does not reflect the natural course of the disease as the model does not capture or present the impact of phenylalanine control on long term clinically meaningful patient outcomes. Prior history of time spent in either the uncontrolled or asymptomatic health states particularly in developmental years and its subsequent impact on health outcomes were not considered. In addition, the NCPE has concerns regarding health related quality of life estimates and the manner in which direct health care utilisation and subsequent costs associated with PKU were accrued in the model. The NCPE considered the submitted cost effectiveness analysis contained inappropriate assumptions

and implausible parameters. The incremental cost effectiveness ratios (ICERs) for the applicant's preferred base case and associated scenario analyses are presented below for information purposes. However the NCPE recommends that the results from the cost utility model presented below are interpreted with caution.

Scenarios modelled	Incremental cost	Incremental QALY	ICER
Base case – uncontrolled and partially controlled			
Phenylalanine tolerance (20%) (base case)	€8,749,188	252.59	€34,638
Phenylalanine tolerance (23%)	€6,481,253	252.59	€25,659
Phenylalanine tolerance (0%)	€23,868,754	252.59	€94,496
All eligible patients			
Phenylalanine tolerance (20%)	€569,733,540	252.59	€2,255,558
Phenylalanine tolerance (23%)	€567,465,605	252.59	€2,246,580
Phenylalanine tolerance (0%)	€584,853,105	252.59	€2,315,416
Asymptomatic patients			
Phenylalanine tolerance (20%)	€279,054,697	252.59	€1,104,769
Phenylalanine tolerance (23%)	€276,786,762	252.59	€1,095,791
Phenylalanine tolerance (0%)	€294,174,262	252.59	€1,164,627
Controlled patients			
Phenylalanine tolerance (20%)	€227,691,672	252.59	€901,425
Phenylalanine tolerance (23%)	€225,423,738	252.59	€892,446
Phenylalanine tolerance (0%)	€242,811,238	252.59	€961,283
Uncontrolled patients			
Phenylalanine tolerance (20%)	€7,832,438	252.59	€31,008
Phenylalanine tolerance (23%)	€5,564,504	252.59	€22,030
Phenylalanine tolerance (0%)	€22,952,004	252.59	€90,866

Table 1: Incremental cost effectiveness ratios

4. Budget impact of sapropterin dihydrochloride

Of the 734 patients identified with PKU in Ireland who are presently under Hospital care, the applicant estimates that 12 adult and paediatric patients with uncontrolled or partially uncontrolled PKU will be eligible for treatment in year 1 following a BH4 response test, a patient compliance rate of 78% with sapropterin dihydrochloride and a 50% market uptake. The number of eligible patients is assumed to increase in year 2 and beyond due to an increase in market uptake. Estimates provided by the applicant indicate that 25 patients will be eligible for treatment in year 2 up to 27 patients in year 5. The applicant states that BioMarin Europe Ltd. will absorb the costs of a one month BH4 treatment trial to determine BH4 responsive status of patients. The NCPE consider that a 6 month treatment trial is a

more appropriate timeframe to produce objective data regarding long term BH4 responsiveness, as recommended in the European PKU guidelines 2017.

The NCPE considered the submitted budget impact model contained inappropriate assumptions and parameters which are not robust. The company estimate that the gross budget impact of both dietary intervention and sapropterin dihydrochloride treatment in PKU is associated with a 5 year cost of €37.41 million. The net budget impact presented by the applicant following the introduction of sapropterin dihydrochloride is €12.91 million over 5 years and is based on the assumption of a 20% increase in phenylalanine tolerance leading to a decrease in dietary products consumed by patients with uncontrolled and partially uncontrolled PKU. The NCPE has updated the budget impact model with revised budget impact estimates including the applicant's assumptions of 100% market uptake and a 68% compliance rate as included in the cost utility model. The gross budget impact associated with sapropterin dihydrochloride in isolation from dietary intervention in patients with uncontrolled and partially uncontrolled PKU is €8,613,217 over 5 years. A conservative estimate of a 100% compliance rate and market share increases the budget impact to €12,666,445 over 5 years. As robust estimates of cost offsets associated with increased phenylalanine tolerance could not be validated by the NCPE, a conservative estimate of net budget impact is estimated to be equivalent to gross budget impact.

A patient group submission was received from The PKU Association of Ireland (PKUAI), and was included in full in the final report to the HSE.

5. Conclusion

As the applicant has failed to demonstrate that sapropterin dihydrochloride is a cost-effective therapy for patients with PKU, reimbursement is not recommended.