# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Sapropterin for treating hyperphenylalaninaemia in phenylketonuria

## 1 Recommendations

1.1 Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin (response as defined in the summary of product characteristics) in people with phenylketonuria (PKU), only if they are:

- under 18 and a dose of 10 mg/kg is used, only using a higher dose if target blood phenylalanine levels cannot be achieved at 10 mg/kg
- aged 18 to 21 inclusive, continuing the dose they were having before turning 18 or at a maximum dose of 10 mg/kg
- pregnant (from a positive pregnancy test until birth).

Sapropterin is recommended only if the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with sapropterin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

PKU is an inherited condition that causes raised levels of phenylalanine in the blood. Without treatment, this causes irreversible brain damage in babies and children and

can affect brain function in adults. The only treatment for PKU is a diet to manage phenylalanine and overall protein intake (protein-restricted diet) and prescribed supplements. The diet is challenging and time-consuming, so it is difficult for some people to maintain. Sapropterin, plus a protein-restricted diet, is used for people whose PKU has been shown to respond to it. The aim of treatment is to maintain satisfactory blood phenylalanine levels to reduce PKU symptoms and complications, and potentially allow a less restricted diet.

Clinical trial evidence compares sapropterin plus a protein-restricted diet with diet alone. It shows that sapropterin effectively reduces blood phenylalanine levels in the short term for people whose PKU has been shown to respond to it, but it is uncertain how well it works in the long term. There is no clinical trial or registry evidence to show how much sapropterin reduces the need for a protein-restricted diet, or how it affects quality of life or brain development.

In people under 18, treatment for PKU is particularly important because of the higher risk of irreversible brain damage to the developing brain. This risk is highest in younger children, particularly up to age 12. Sapropterin may reduce the risk of brain damage for these children, but there is no clinical evidence to confirm this, and this potential benefit is not captured in the cost-effectiveness estimates. Taking uncaptured benefits and the clinical evidence into account, cost-effectiveness estimates are acceptable at the upper limit of what NICE considers an acceptable use of NHS resources. Sapropterin is therefore recommended for people under 18. The dose for children can be increased above the starting dose of 10 mg/kg, only if target blood phenylalanine levels are not achieved at a dose of 10 mg/kg. So, it is recommended for treating PKU in people under 18, normally at a dose of 10 mg/kg.

Stopping treatment and relying on diet alone at 18 years old is not clinically ideal. It would benefit young adults if treatment with sapropterin could be continued for as long as possible during final brain development and transition into adulthood. Taking this into account the maximum age at which sapropterin can be considered a cost-effective use of NHS resources is 21. However, for this use to be cost effective people would need to continue the dose they were having when they were under 18.

In practice this may mean that some young adults may need more dietary control alongside sapropterin between the ages of 18 and 21 (inclusive) than they would with a higher dose. Sapropterin is recommended for people aged 18 to 21, continuing the dose they were having before turning 18. People who have not had sapropterin before turning 18 can still have it until they turn 22. But the purpose of recommending sapropterin for this age group is to allow more control of phenylalanine levels while transitioning from sapropterin to dietary control alone by age 22, when the brain is nearly fully developed.

The risk of irreversible brain damage reduces with age, particularly after brain development is complete. So the adverse effects of being unable to follow the protein-restricted diet are considerably reduced in adults compared with the risks in childhood. Adults may still gain considerable benefit from sapropterin because of fewer symptoms related to raised phenylalanine levels, without having to follow the protein-restricted diet as strictly. However, these benefits are included in the economic modelling. Also, in adults the weight-based dose together with the higher average mg/kg dose results in costs that are considerably higher than in children, but the benefits are not correspondingly higher for adults. Even taking into account any uncaptured benefits in adults, the cost-effectiveness estimates are substantially higher than what NICE considers an acceptable use of NHS resources. So, it is not recommended for adults after they reach the age of 22.

Raised phenylalanine levels in pregnant women with PKU can cause severe birth defects in their unborn children. This could increase maternal anxiety, with the additional burden of the even more restrictive diet that is needed during pregnancy to maintain the stricter recommended phenylalanine levels. There is not enough evidence to predict how much sapropterin might prevent harm to the unborn child. If the risk of major harm is reduced, which is possible, then there are likely to be major lifelong benefits for the unborn child. The benefits for the pregnant woman with PKU who has the treatment are included in the cost-effectiveness analysis, but benefits for the unborn child have not been included. Taking the benefits for both these individuals into account, the cost-effectiveness estimates are likely to be within what

NICE considers acceptable. So, sapropterin is recommended during pregnancy until birth.

# 2 Information about sapropterin

## Marketing authorisation indication

2.1 Sapropterin (Kuvan, BioMarin) is indicated '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'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

## Price

2.3 The list price of sapropterin is £597.22 per 30-tablet pack. Each tablet contains 100 mg sapropterin dihydrochloride (excluding VAT; BNF online, accessed January 2021).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes sapropterin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

# 3 Committee discussion

The appraisal committee considered evidence submitted by BioMarin, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

## The condition

### PKU is associated with high blood phenylalanine levels that can lead to irreversible damage to the developing brain

3.1 Phenylketonuria (PKU) is a rare, inherited metabolic disorder caused by mutations in the phenylalanine hydroxylase (PAH) gene. Mutations of the PAH gene result in reduced activity of the PAH enzyme, which is responsible for breaking down the amino acid phenylalanine (Phe) to tyrosine. The reduced activity of PAH means that people with PKU are unable or less able to break down Phe, leading to increased levels in the blood. High blood concentrations of Phe are toxic for the brain and can cause irreversible damage during brain development. The European PKU guidelines recommend target blood Phe ranges of 120 to 360 micromoles per litre for children up to age 12, and 120 to 600 micromoles per litre for people aged 13 and over, recognising the particular risk in children under 13. Around 1 in 10,000 babies are diagnosed with PKU in the UK each year and there are currently about 2,000 people with PKU in NHS care in England. Childhood is the most critical period for brain development. Therefore, high Phe concentrations during this period can lead to long-term disability such as a severe learning disability, microcephaly (smaller head size than expected), seizures and tremors, stunted growth, delayed speech and reduced executive function (working memory, flexible thinking, and self-control). To avoid long-term brain effects in children with PKU, current treatment in the NHS consists of a protein-restricted diet and dietary supplements to control blood Phe levels. This diet should be continued as an adult. Clinical experts noted that poor control of blood Phe levels during childhood and the resulting irreversible brain damage can then mean that some adults who have been affected are less able to follow the diet. One patient expert confirmed that there are adults with PKU in the National Society for Phenylketonuria (NSPKU) who have severe symptoms and irreversible brain damage. Clinical experts explained that brain development peaks at around age 12. After this, high

Phe levels are unlikely to affect IQ. However, young people above this age may still be at some risk of less severe long-term brain damage from high Phe levels, because brain maturation is probably not complete until around age 25. The committee concluded that PKU is associated with high blood Phe levels that can lead to irreversible damage to the developing brain.

## High blood Phe levels in adults with PKU can affect the brain but the risk of new irreversible damage is less than in children

3.2 In adults, high Phe concentrations can result in short-term symptoms, which are considered largely reversible by lowering Phe levels through adherence to diet. These include impaired executive function, reduced autonomy, impaired social maturity, difficulty forming relationships and neuropsychiatric symptoms such as depression, anxiety, and inattention. Clinical experts estimate that many adults with PKU find it difficult to maintain good control of blood Phe levels. However, one clinical expert noted that from their research many adults with PKU who have had treatment in the NHS have quality of life and academic and employment performance within the normal range. This is despite some evidence of impaired executive function, and some no longer following the diet. The experts noted that timing, duration, and intensity of exposure to high Phe levels in childhood and adolescence determine the severity of symptoms and long-term brain effects experienced by people with PKU. The committee also noted comments received in response to consultation that symptoms experienced by adults with PKU may not be completely reversible when a protein-restricted diet is restarted or adhered to more closely. Also, it was stated that brain development continues beyond the age of 18, possibly until 25 or even 30. The clinical experts explained that some neuropsychological outcomes are improved when Phe levels are reduced with diet, which suggests that some of the changes are reversible. While there could be the potential for subtle brain damage to happen between 18 and 25 in people with PKU, there is little evidence to

confirm or quantify this. Also, the clinical experts agreed that patients were unlikely to suffer significant or permanent harm by stopping sapropterin treatment at 18 rather than 25. However, patient experts stated that the chronic effects of high Phe levels on the adult brain cannot be ignored or undermined, particularly when they lead to significant damage or deteriorating mental health outcomes such as depression and anxiety. The clinical experts acknowledged that some adults with PKU have brain damage because of high Phe levels, but there is no systematic evidence available to quantify the effects of high Phe on the adult brain or whether damage is irreversible in adults. One clinical expert noted that it is challenging to determine if brain damage is caused by high Phe levels in childhood (when the brain is still developing) or in adulthood. This can be further complicated by non-PKU-related brain damage that can happen because of nutritional deficiencies such as lack of vitamin B12. However, patient experts highlighted that any treatment that allowed patients to follow a less restricted diet could also alleviate damage from nutritional deficiencies. Another clinical expert stated that the effects of Phe on the brain can differ widely among adults with PKU. For example, some people experience brain effects within a few months of having high Phe levels compared with years for other people, and some people experience brain effects even when Phe levels are not particularly high. The committee accepted that high blood Phe levels in adults can affect the brain and may lead to brain damage. However, because brain development peaks at age 12, it concluded that the risk of irreversible damage decreases after that age and is less in adults than in children.

## High blood Phe levels in pregnancy can have harmful effects on the unborn child

3.3 In pregnancy, high blood Phe levels can have harmful effects on the unborn child and lead to abnormal development. These effects include birth defects such as congenital heart disease and heart defects, microcephaly, a learning disability, delayed learning and development,

permanent brain damage, low birth weight, miscarriage, attention deficit hyperactivity disorder and autism spectrum disorders, impaired growth and impaired learning ability. Clinical experts explained that the effects of maternal PKU syndrome can be worse than the effects of PKU itself because the unborn child is exposed to high Phe levels which are teratogenic, during a crucial phase of development. The European PKU guidelines recommend pregnant women's Phe levels should stay between 120 and 360 micromoles per litre. Also, the committee heard from the experts that in practice good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible. This is very challenging to maintain with diet alone. The experts explained that Phe levels should be kept low throughout the whole pregnancy and that every 60 micromoles of Phe per litre over the 360 micromoles per litre target results in about a 3-point IQ reduction for the unborn child. Dietary measures should ideally be started before conception to avoid congenital effects, but at least at the earliest possible opportunity to avoid harmful effects on the unborn child. Comments received in consultation indicated that women who are trying to become pregnant find achieving the target Phe levels safe for pregnancy very difficult using protein-restricted diet because of the much stricter levels compared with what they are normally used to. Also, women find it difficult to maintain very low Phe levels for long periods of time before becoming pregnant and during pregnancy. As a result, some women are fearful of becoming pregnant or completely stop having intimate or sexual relationships because of worries that they may not be able to cope with the protein-restricted diet during pregnancy and harm their unborn child. At the first committee meeting, a patient expert highlighted that there is an NHS policy in place for providing sapropterin for pregnant women with PKU. The NHS England commissioning expert and the patient expert indicated that the current NHS policy only covers pregnant women with PKU who are unable to establish safe Phe levels for the unborn child (100 to 360 micromoles per litre) on a protein-restricted diet. Only then can they be tested for a

response to sapropterin. The experts stated this delay in starting sapropterin can result in the unborn baby being exposed to high Phe levels in the critical phase of early pregnancy before sapropterin is given. The patient and clinical experts highlighted that treatment with sapropterin is started too late in clinical practice because women with PKU must first show that they cannot achieve recommended Phe levels on diet alone. A clinical expert stated that the outcomes for unborn children are much better if blood Phe levels are brought down very early, within the first 6 weeks of pregnancy, before the organs start developing. They stated that in practice this approach is more likely to work when pregnancies are planned, and pre-conception plans can be developed with the woman's metabolic teams. The NHS England commissioning expert agreed that the current NHS policy for sapropterin works better for planned pregnancies than unplanned ones. Patient and clinical experts stated that about half of pregnancies in women with PKU are unplanned, which is similar to the rate seen in the general population. The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child and this causes tremendous anxiety for many women with PKU. Early control of phenylalanine levels in all pregnancies was desirable to minimise the risk of PKU syndrome in the unborn child, with potential lifelong consequences for the child. The committee noted that the importance of protection of the unborn child had already been recognised by the NHS in NHS England's policy to provide sapropterin for some pregnant women.

## Treatment pathway

### The only treatment option available for people with PKU is a self-managed protein-restricted diet

3.4 Current clinical management of PKU is through a lifelong protein-restricted diet. This consists of prescribed low-protein and Phe-free medical foods to help reduce natural Phe consumption, and Phe-free

amino acid supplements to improve nutrition and prevent nutritional deficiencies. The protein-restricted diet also involves reducing natural protein consumption according to individual Phe tolerance. Clinical experts stated that 80% of people with PKU can tolerate less than 10 grams of protein per day, equal to 1 or 2 slices of bread. To adhere to a protein-restricted diet, people with PKU must avoid foods and drinks containing protein or aspartame, which can be converted into Phe. This includes foods that are rich in protein (for example, meat, fish, dairy products and soya), foods with less natural protein (for example, fruit, vegetables, cereals, flour or pasta) and alcoholic drinks containing protein (for example, beer and stout). People with PKU routinely take blood samples at home, which are then sent to a central laboratory to measure blood Phe levels. A healthcare professional provides blood Phe concentration level results through a telephone consultation and, if necessary, will give advice on adjusting the diet to manage blood Phe concentration levels. The committee concluded that the only treatment option available for people with PKU is a self-managed protein-restricted diet.

## People with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet

3.5 The primary aim of clinical management and the protein-restricted diet is to prevent irreversible and reversible brain damage by keeping blood Phe concentration levels within the ranges recommended in European guidelines. However, both clinical and patient experts highlighted that people with PKU may be outside recommended Phe ranges. In childhood, the dietary restrictions put great pressure on carers and families because of the constant fear of irreversible damage. Adults can have raised Phe levels because they struggle to adhere to, or have completely stopped, their diet. Clinical experts noted that around 50% of adults with PKU are on a protein-restricted diet. Patient experts explained that being on a strict

protein-restricted diet is burdensome and demanding for people with PKU and their carers for several reasons:

- The time-consuming nature of food shopping and meal preparation. Also, the wide range of skills needed to understand food labels, calculate precisely, and weigh the amount of Phe in different foods that can be eaten in each meal, and prepare and cook meals regularly. This can take 2 to 3 times as long as normal and make managing the diet a dominant activity of daily life.
- Poor taste and disagreeable smell and texture of low-Phe foods and synthetic protein substitutes. These have to be taken in large volumes 3 to 4 times a day and can cause digestive problems.
- Costs of 'free-from' foods and difficulties accessing prescription food because of limits on which low-protein foods can be prescribed, as some are considered luxury items.
- Problems such as weight gain resulting from the high carbohydrate content of the protein-restricted diet.

At the second committee meeting a clinical expert highlighted research that suggests that 5% of adults with PKU have comorbidities unrelated to PKU such as cystic fibrosis, cancer, type 1 diabetes, renal insufficiency and inflammatory bowel disease. This makes sticking to the diet very difficult. It has also been reported that people with PKU are 4 times more likely to have other conditions such as a learning disability, autism spectrum disorder, eating disorders, bipolar and epilepsy than the general population, which also make it harder to follow the diet. Comments received in consultation also advised that a further contribution to overall reduced health is the constraints of a restricted diet on exercise. In particular, the low-protein diet makes it difficult to achieve satiety from food, which leads to many adults reporting high levels of fatigue before and after exercise. This limits people's ability to lead a healthy lifestyle and may account for the higher rates of comorbidities such as diabetes mellitus and ischaemic heart disease. Comments from consultation also

indicated that poor housing stability, lower household income and being a member of Gypsy, Roma and Traveller communities could affect people's ability to stick to the PKU diet. Other consultation comments noted that diet can be very expensive even when the cost of low-protein foods and amino acid supplements are not taken into account. For example, people with PKU end up spending more money on protein-free healthier foods and ingredients to keep their diet varied and palatable, to make it easier to stick to. In addition, because of the high sugar content of the PKU diet people also experience teeth issues and need regular dental care, whether that is provided through the NHS or privately. Living arrangements and availability of storage space can also cause difficulties with sticking to the diet. PKU diets involve cooking all meals from scratch so need cooking facilities and equipment, and ample storage for medication, Phe-free foods, amino acid supplements and kitchen equipment. In some cases, this needs as much as an entire room just for storage, but this is not always available when living in small or shared accommodation. The committee understood that carers of children with PKU also report additional difficulties related to diet management. These include strains on their relationships, struggling to get the right support, and having to give up work or working part-time to dedicate more time to diet management. They also need to educate professionals, teachers, other children's parents, their families, and other carers about PKU and the diet restrictions. The known risk of irreversible brain damage if Phe levels are not controlled is a permanent source of stress for parents. The committee concluded that the protein-restricted diet was extremely burdensome and difficult to stick to, and people with PKU and their carers would welcome a treatment that allows a less strict protein-restricted diet.

## Experiences of people with PKU and their carers

### There is a need for a treatment that can reduce Phe levels and give people with PKU and their carers peace of mind

3.6 Many adults describe the effects of high Phe levels as 'brain fog', forgetfulness, tiredness, confusion, low mood and feelings of irritability. This can affect their ability to control their diet and maintain appropriate blood Phe levels. Additionally, adults with PKU may find it difficult to juggle work, studies and family commitments with controlling their diet and maintaining Phe levels. Some adults are unable to engage in full-time work because it creates a vicious cycle of less time to control diet and higher Phe levels, leading to reduced ability to focus and organise the diet. In addition, they can have a sense of being dependent on other people for support, feel socially isolated and constantly worry about maintaining their diet (see section 3.5). The committee noted that people with PKU have higher rates of comorbidities than the general population. The comorbidities seen more often in adults with PKU are: chronic ischaemic disease, urticaria, oesophageal disorders, gastroesophageal reflux disease, gastritis, anaemia, obesity, asthma, renal insufficiency, eczema, alopecia, osteoporosis, rhinitis, gall bladder disease and kidney calculus. Studies suggest that high Phe levels in people with PKU could be associated with biological mechanisms that increase the risk of chronic diseases. Also, the PKU diet, medical food and nutritional deficiencies because of the PKU diet may also contribute to the increased risk of chronic diseases. Consultation comments reiterated that PKU and the PKU diet have a substantial effect on all aspects of adults' lives. The patient and clinical experts advised that adults with PKU who have the best health outcomes typically have support from family, friends, partners, and carers.

Concerns about high blood Phe levels can also affect other groups of people with PKU, some of whom have characteristics protected under the Equality Act 2010. These include:

- **Women:** PKU can affect women's sexual and reproductive health and choices. In some cases, women completely forego sex because they are afraid of becoming pregnant and accidentally harming their unborn child (see section 3.3).
- **Pregnant women:** Pregnant women with PKU describe pregnancy as traumatic because of the strictness of the PKU diet and the anxieties and stress of high Phe levels harming their unborn child (see section 3.3). Mothers with PKU describe being unable to cope with the pressures of strict dietary management while caring for their child, and experiencing anxiety, depression and inability to focus as a result.
- **Children:** PKU is very limiting for children, who face isolation and feel restricted in their ability to join social events such as school trips, festivities, travelling, or meals out because of their diet. Children, as well as adults with PKU, frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) because of high Phe levels. At the second committee meeting, a patient expert highlighted how vulnerable families often struggle to control their child's Phe levels.
- **Young adults:** In response to consultation, stakeholders and members of the public did not agree with the draft recommendation to stop sapropterin at 18 years of age. Consultation comments stated that high Phe levels can exacerbate the difficulties that young adults face as they transition from adolescent to adult life. Some young adults are in the process of moving out of their parents' home, undertaking further education, starting jobs, and learning to live independently. All of this can be affected by symptoms of high Phe levels or having to deal with

the challenges of organising and maintaining the PKU diet without the support of their parents or carers for the first time. The committee also heard that as young adults transition from child clinical services to adult services, they may have reduced support from metabolic teams. One patient expert gave an example that the clinic her adult children attend is not equipped to support all patients appropriately because it is an add-on to an existing diabetes clinic. One clinical expert indicated that people with PKU may not be well supported in their transition from child to adult services unless they are seen in a big centre. Patient and clinical experts explained this is because some adult clinical services are not well resourced or have the right kitchen space and equipment to support all adults with PKU across the country. However, one expert noted that some of the larger metabolic centres did include metabolic kitchens for adults. A clinical expert also highlighted that most adult clinics tend to focus on supporting pregnant women with PKU rather than all adults. The committee appreciated that a recommendation to stop treatment at 18 years of age would mean people have to begin managing Phe levels through diet alone for the first time at that age, which would not be ideal. The committee has recommended treatment until people reach the age of 22, but it could only recommend sapropterin for people aged 18 to 21 (inclusive) at the dose they had when they were under 18 (and not escalating to the adult dose). It recognised that for some young adults this may mean the dose they have is considered a tapering dose and so dietary control may still need to increase at age 18. However, while that may be challenging it is inevitable for any age-based recommendation, and the committee had no evidence that this would be harder to manage at age 18 or 22, rather than at any older age. Also, the reason for the committee's recommendation that treatment should stop at age 22, considered as a tapering off of sapropterin from age 18, was related to the underlying biology of brain development and diminishing irreversible risk with age, associated with the higher treatment costs in adults. Having examined

the options up to age 25, 21 was the maximum age that treatment could be considered cost effective.

- **Disabled adults:** High Phe levels in adults with PKU- and non-PKU-related disabilities can lead to severe behavioural problems. At the second committee meeting, one clinical expert explained that people with late-treated PKU who have sustained long-term brain damage have a lifespan that is severely reduced by almost 20 years compared with the general population. Patient and clinical experts also highlighted that people with late-treated or untreated PKU have severe behavioural problems, strict food habits or food neophobia. This results in challenges managing the PKU diet and blood Phe levels, additional nursing and care home needs, and other costs. One patient expert confirmed that there are extreme examples of people with PKU who need more care, attention and support because of severe behavioural problems, in some cases even needing to be restrained. The patient expert added that reducing Phe levels in these people would be expected to lead to less challenging care provision and reductions in care plans, need to calculate natural protein 'exchanges' and close supervision of either the person themselves or what they eat. The committee was mindful that some disabilities may mean that adults are less able to adhere to the PKU diet and therefore these people would possibly get more benefit from sapropterin.

The committee noted the many personal stories that had been received in response to consultation. It concluded that there is a clear need for a treatment that could reduce Phe levels, allow a less restricted diet, and give people with PKU and their carers peace of mind. However, the appraisal process requires that the costs of the treatment must be taken into consideration in relation to the benefits shown.

## Sapropterin is clinically appropriate and beneficial for people with PKU that responds to sapropterin

3.7 Sapropterin is a synthetic version of the naturally occurring tetrahydrobiopterin. The marketing authorisation for sapropterin is for adults and children of all ages with PKU that has been shown to be responsive to such treatment. Response to sapropterin is determined by a reduction in blood Phe levels. Blood Phe levels are checked before sapropterin treatment and weekly after starting treatment for 1 month. Response is defined as a reduction in blood Phe levels of at least 30% or achieving blood Phe levels defined for an individual patient by the treating physician. One clinical expert highlighted that there is a need for clearer response criteria to define who would benefit most from sapropterin. Another clinical expert noted that there is a response relationship between sapropterin and the levels of PAH activity and mutations. However, mutation analysis is not routine practice in the UK. The company estimated that 391 people with PKU in England and Wales are eligible, consisting of 366 current patients and an increase of 25 patients with PKU each year. Patient experts advised that adults with PKU who have taken sapropterin report improved day-to-day functioning, particularly concentration and mood. In addition, they were able to resume other activities such as studies or work. Parents of children with PKU report similar benefits in the mood, energy, concentration and behaviour of their children. They also report large increases in natural protein consumption, with children having a wider and more socially normal diet and greater freedom to participate in social activities. In addition, sapropterin also led to health benefits in children. These included increased bodyweight and growth, improvements in gastrointestinal symptoms and fewer mouth ulcers. Carers of people with PKU reported a significant easing of burden of care. This included not needing to prepare special prescribed low phenylalanine foods and being able to delegate childcare to others for first time. Some carers reported being able to return to work or study, increase working hours, spend more time with other children, and have time for

other family responsibilities. At the second committee meeting, an expert stated that using sapropterin could prevent a child being taken into care because it could keep the child's Phe levels within the target range for families struggling to follow the diet. The committee concluded that sapropterin could be highly beneficial for those people with PKU that responds to sapropterin.

## Clinical effectiveness

### The trial evidence shows sapropterin plus protein-restricted diet is clinically effective compared with protein-restricted diet alone

3.8 Evidence for the clinical effectiveness of sapropterin plus protein-restricted diet came from several randomised controlled trials (RCTs). These included 3 double-blind studies and 1 open-label study. The number of people in the studies was between 56 and 206 and the RCTs were short, between 6 and 26 weeks. The population included was different across the RCTs according to age, response to sapropterin and blood Phe concentration levels at screening stage. In 3 of the RCTs, sapropterin plus protein-restricted diet was compared with either placebo plus protein-restricted diet or protein-restricted diet alone. Results from the RCTs show that people having treatment with sapropterin plus protein-restricted diet had significantly reduced blood Phe concentration levels and maintained target levels compared with people having diet only. They also increased or maintained their consumption of natural Phe compared with people having treatment with protein-restricted diet. However, none of the RCTs were included in the company model because of their short duration and small sample sizes. The committee agreed that this was appropriate but concluded that the available trial evidence shows that sapropterin in combination with a protein-restricted diet is clinically effective compared with protein-restricted diet alone.

## The PKUDOS registry has evidence for long-term efficacy of sapropterin plus protein-restricted diet for the whole PKU population and is generalisable to the NHS

3.9 The company presented evidence for long-term efficacy of sapropterin from 2 multicentre registries. These are the PKUDOS registry in the US and the KAMPER registry in 8 European countries. The PKUDOS registry enrolled 1,922 people while KAMPER enrolled 576. Follow up was up to 9 years at the time of the most recent interim analyses. KAMPER includes people whose PKU was shown to respond to sapropterin or tetrahydrobiopterin and who were having sapropterin. But it does not provide a comparison with protein-restricted diet alone. In addition, 83.5% of those enrolled in KAMPER were children (under 18) and only 16.5% were adults. People were enrolled in the PKUDOS registry if they had blood Phe levels over 360 micromoles per litre and had previously had sapropterin, were currently having sapropterin, or were due to have sapropterin within 90 days of enrolment. In the PKUDOS study 59.1% of people enrolled were children (under 18) and 40.8% were adults. The company used data from 191 people who were due to have sapropterin within 90 days to represent the sapropterin plus protein-restricted diet cohort in the economic model. There were 160 people who had previously had sapropterin before enrolling or stopped taking it while in the registry, who were considered to represent the protein-restricted diet cohort. The committee concluded that only the PKUDOS registry provides evidence for long-term efficacy of sapropterin plus protein-restricted diet compared with diet alone in the whole PKU population. One clinical expert highlighted that people included in the PKUDOS registry may differ from adults with PKU in the NHS because of difficulties in obtaining the protein-restricted diet in the US. The committee reasoned that everyone enrolled in the PKUDOS registry, both those on diet alone and those having sapropterin plus diet, would be equally affected by difficulties in obtaining a protein-restricted diet. Therefore, the relative benefit seen would be a fair estimate of the relative benefit that would be seen in the NHS, where

both groups would have equal access to the diet. It concluded that people with PKU enrolled in the PKUDOS registry were likely to reflect people with PKU in the NHS.

### The results of the PKUDOS registry are likely to be generalisable to NHS clinical practice

3.10 Results from the PKUDOS registry show the proportion of people achieving Phe levels between 120 and 360 micromoles per litre were similar over time for all age groups. Higher proportions of people achieved target Phe levels in the younger age subgroups (under 4 and under 12) than adults (18 and over). However, the committee noted that this is expected because the target range of 120 to 360 micromoles per litre is for children under 12 and the target for adults is up to 600 micromoles per litre. The proportion of people achieving target Phe levels between 120 and 600 micromoles per litre were similar across the under 4 and 18 and over age groups but decreased for the under 12 and under 18 groups over time. Higher proportions of people achieved target Phe levels between 120 and 600 micromoles per litre in younger age subgroups (under 4, under 12 and under 18) than adults (18 and over). The committee noted that for each target range the numbers of people contributing long-term data at 9 years were small (between 4 and 52 people). It also recalled that people were assigned to age group based on age at registry enrolment. One clinical expert explained that the results should be interpreted in the context of a protein-restricted diet. That is, the baseline proportions of people achieving target Phe levels are based on Phe control with protein-restricted diet alone. Therefore, people taking sapropterin in addition to protein-restricted diet are able to maintain and achieve target Phe levels long-term while increasing natural protein consumption and reducing supplements. The committee concluded that the results of the PKUDOS registry are likely to be generalisable to NHS clinical practice.

### The sapropterin dose used in clinical practice in the UK would be in line with the NHS England impact assessment report for sapropterin

3.11 The company stated that the mean dose of sapropterin for children is 10 mg/kg and the mean dose for adults is 12.5 mg/kg, according to the NHS England Integrated Impact Assessment Report for sapropterin. The committee noted that the total dose given was not just age related but also weight related, that is, per kg body weight. Because average adults have a higher kg weight than the average child, there are 2 factors which result in much higher drug costs for adults than children and mean that the annual drug costs for adults are 3 times higher than for children. The ERG was concerned that the doses of 10 mg/kg and 12.5 mg/kg for children and adults suggested by the company are underestimates of the doses used in clinical practice. In KAMPER, the average sapropterin dose was 12.7 mg/day and this included 83.5% children under 18 (see section 3.9). In the PKUDOS registry the average dose was 18.7 mg/kg and around 60% of people were under 18 (see section 3.9). The company indicated that sapropterin dosages in the KAMPER registry were left to the discretion of the treating clinicians, so they reflect clinical practice in the 8 European countries that contribute to the registry. Clinical experts highlighted that European clinical practice is likely to be similar to UK practice. Clinical experts explained that the difference in mean dose between PKUDOS and KAMPER is because clinicians in the US use lower blood Phe targets than in Europe and will use any sapropterin dose necessary to achieve those targets. In contrast, in Europe, target Phe levels and sapropterin response are not well defined and clinicians are more cost-sensitive because they must justify using higher doses of sapropterin. The committee noted that if outcome data from PKUDOS were used, then logically the same dose should be used to ensure the same efficacy. However, the company estimated an average dose for children of 10 mg/kg and 12.5 mg/kg for adults. The committee noted that although this was lower than the average doses in the PKUDOS registry, it corresponds to the doses in the NHS England Integrated Impact

Assessment Report for sapropterin. One clinical expert stated that in their experience using between 10 mg/kg and 20 mg/kg resulted in little difference in outcome. Clinical experts further explained that increasing sapropterin dose does not improve efficacy because response to sapropterin primarily depends on the level of PAH activity and mutations, not the dose. They highlighted that people whose PKU responds to sapropterin increase their tolerance to natural Phe consumption by 2 to 4 times, regardless of dose. All clinical experts agreed that it is not just blood Phe levels that are important, but also the amount of natural protein that can be consumed. The committee concluded that the sapropterin dose per kg used in clinical practice in the UK is likely to be in line with the NHS England impact assessment report.

### The estimate of 71.2% reduction in protein-restricted diet is not evidence-based and could be an overestimate

3.12 The company assumed that people taking sapropterin with controlled blood Phe levels can relax their protein-restricted diet with a 71.2% reduction in protein supplements and low-protein food. This is important because savings can offset the costs of sapropterin treatment. The ERG noted that it could not determine the robustness of the methods used to calculate this value. Clinical experts highlighted that some people with PKU who take sapropterin can completely remove protein substitutes from their diet, referencing a forthcoming systematic review. The committee also heard from the company that a study in Netherlands (Evers et al. 2018) has shown that, over 5 years, patients had an average 68% reduction in amino acid supplements. However, one clinical expert cautioned that the results of the studies are likely to be influenced by clinical practice and the definition of sapropterin response used in the country of study. For example, in Switzerland it is recommended that only people with PKU that responds very well can have sapropterin. Therefore, everyone who has sapropterin would be expected to completely eliminate protein substitutes. The committee concluded that it seemed likely that

people would reduce their protein-restricted diet, but it could not be sure that the reduction would be as high as 71.2%.

## Long-term brain damage happening in childhood is an important aspect of PKU

3.13 Irreversible brain damage in people with PKU can manifest as:

- lower IQ score compared with people without PKU or unaffected relatives
- clinically relevant neuropsychological impairments (about 25% of people with PKU)
- minor neurological symptoms such as tremor, brisk lower limb reflexes, mild motor impairment (20% to 40% of people with PKU).

Additional care needs for people with PKU and long-term brain damage can include: additional blood Phe monitoring, hospital appointments and telephone contacts by health professionals, possible hospital admissions, education, health and care plans for learning needs, additional teacher and teaching assistant time to supervise protein substitutes (for all children with PKU), use of home support workers and possible involvement of safeguarding and social services such as referral to early help services for people with very poor phenylalanine control (according to European PKU guidelines). However, information is not routinely collected on long-term brain damage because of PKU, or the number of children referred to early help services and social services, and the costs involved. The committee concluded that long-term brain damage because of high Phe levels in childhood is an important aspect of PKU and has a substantial effect on quality of life. However, while there is an expectation that sapropterin would reduce the risk of permanent damage, there is no direct evidence to substantiate or quantify any long-term benefit.

## The company's economic model

### The model time horizon is not long enough to capture any effect of sapropterin on long-term brain damage, and the model is not appropriate to capture the effects of PKU in pregnancy

3.14 The ERG had concerns about the company's original model. So, after technical engagement the company submitted a new decision tree model with a 1-year time horizon to estimate the cost effectiveness of sapropterin plus a protein-restricted diet compared with protein-restricted diet alone. The model cohort was split into sapropterin plus diet and diet alone arms and included 3 health states for each group based on symptom severity (mild, moderate, and severe). The company added additional utility weighting for a learning disability (none, mild and moderate). The ERG explained that the 1-year time horizon was appropriate for the model because of a lack of data for long-term brain damage and because registry data showed that the benefits associated with sapropterin only happen while a person takes sapropterin. Therefore, the model focused on the drivers of the cost effectiveness of sapropterin plus a protein-restricted diet compared with a protein-restricted diet. This included reduction in the costs of a protein-restricted diet, a gain in quality of life from not having to follow a strict diet, and potentially a lower PKU symptom burden for people with PKU. None of these, or any other benefits, were captured for the unborn child in pregnant women with PKU. The committee concluded that the model time horizon is not long enough to capture any beneficial effect on long-term brain damage in people with PKU, and the model is not appropriate to capture the effects of PKU in pregnancy.

## Utility values

### The utility values from the time trade-off study are highly uncertain, but are the only available evidence

3.15 Quality of life was not assessed in sapropterin studies because of difficulties in measuring it in people with PKU. The company obtained health state utility values from a time trade-off (TTO) study done in Sweden. It used hypothetical vignettes, which were developed to represent the experience of adults with PKU in the UK and were modified for children with PKU by UK clinicians. The vignettes were valued by a sample of more than 1,000 adults in Sweden from the general population and validated by UK clinical experts (3 specialist adult metabolic physicians, 2 specialist paediatric metabolic physicians, and 1 advanced practitioner in metabolic disease and experienced metabolic dietitian). The ERG and clinical experts acknowledged that quality of life is difficult to measure in people with PKU because of small patient samples and range of disease states. However, the ERG highlighted that the TTO study is not aligned with the NICE reference case, which states that health state measurements should be obtained from patients and valued by the public, whereas hypothetical patient vignettes were used in this study. Despite this, the committee noted that the TTO study is the best available source of utility values for PKU symptom states and, although not necessarily robust, it is the only available evidence.

### The utility reductions estimated for learning disability are not captured appropriately in the company model

3.16 The company captured the effect of irreversible long-term brain damage in the form of IQ reductions (learning disability) resulting from PKU symptoms. It used data from a meta-analysis by Waisbren et al. 2007 in children under 12 with PKU having early treatment (the most critical period for brain development and maturation, see section 3.1). It used this to estimate an average 3-point reduction in IQ per 100 micromole per litre

increase in blood Phe levels and applied it to different symptom severities. The company applied the estimated IQ reduction to moderate and severe PKU symptoms to calculate utility reductions associated with long-term brain damage in the model. However, it applied similar utility reductions to people of all ages, despite children being at higher risk of irreversible long-term brain damage because of increased blood Phe levels. Also, the ERG was concerned that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states (see section 3.15). Furthermore, the committee noted that the long-term effect of brain damage from uncontrolled blood Phe levels cannot be captured in the model because of the 1-year time horizon. It concluded that the utility reductions estimated for learning disability are not captured appropriately in the company model

### The company's methods used to calculate health state utility values are inappropriate and make the utility values highly uncertain

3.17 The company estimated the health state utility values for people with PKU by applying utility reductions because of a learning disability, utility reductions because of PKU symptoms and utility reductions because of protein-restricted diet to the baseline utility values of people without PKU or a learning disability. The estimated utility values for people with severe PKU and on a protein-restricted diet are very low (less than 0.1 and close to the utility associated with death [0]) or negative (state worse than death). The ERG highlighted that very low or negative utility values are unusual, but possible. However, the company did not provide any justification for such low values. The clinical experts pointed out that there are people with severe PKU symptoms and an IQ below 50, but with good care provision their quality of life would not be expected to be so poor as to be close to death. However, one patient expert confirmed that they are aware of a patient with severe symptoms and a learning disability who has communicated that they wish to die on several occasions. Even so, the committee was not persuaded that such low values would be typical of the

patient population. In addition to the extremely low values, the committee was concerned that the company chose to subtract the different utility reductions from baseline under the assumption that they are completely independent of each other. The company explained that utility multiplication methods, which would have accounted for relationships between the different elements, were not possible because of the short time horizon of the model. It also confirmed that learning disability was not captured in the TTO study and was considered independent from the rest of the elements. The ERG only included utility reductions because of PKU symptoms and protein-restricted diet in the protein-restricted diet cohort, which the committee also did not consider ideal. The committee concluded that the company's methods used to calculate health state utility values were inappropriate and make the utility values highly uncertain. However, the committee noted that the differences between the company and ERG estimates of utility values in PKU was not a major contributor to the differences in calculated cost effectiveness.

## The company's added utility gains are not justified and are the key drivers of differences between the company and ERG cost-effectiveness estimates

3.18 The company included additional utility gains for all patients with mild, moderate or severe symptoms having sapropterin. This was over and above the utility gain from reducing PKU symptoms and relaxing the protein-restricted diet, which were included by the ERG. The company did not explain the reasoning behind this added utility gain. The committee noted that for adults some of the values were counterintuitive, for example the added utility gain was the same for people with mild and severe symptoms but less for people with moderate symptoms. The committee concluded that the added utility values were not explained or justified but were key drivers of the differences between the company and ERG's cost-effectiveness estimates.

### The utility gains modelled by the company for all women of childbearing age are not evidence-based, but could be used as a proxy for maternal anxiety and stress experienced during pregnancy

3.19 The company included additional utility gains for all women of childbearing age who have sapropterin, to capture the benefit to the unborn child. The ERG noted that these values are arbitrary, and the company did not give any justification for including them. During the second committee meeting, the company clarified that the additional utility gain for all women of childbearing age represented the anxiety and stress associated with pregnancy and maintaining the lower target Phe levels needed during pregnancy. The ERG recognised that the utility gains included by the company could be used as a proxy for anxiety in pregnancy and that the value used is reasonable but is in the higher range of values. One patient expert indicated that including a higher value would be reasonable when considering that pregnant women with PKU not only have to deal with the stress of pregnancy, but also the worries of miscarriage. The patient and clinical experts added that treatment for PKU in pregnant women could be improved, because they felt the current NHS policy meant pregnant women were having treatment too late (see section 3.2). The committee agreed that with the current NHS policy in place, the effects of uncontrolled Phe levels on the unborn child could be substantial before the woman had access to sapropterin. It considered that the maximum benefit of sapropterin during pregnancy would be obtained by it being available from conception, but this was complicated by the fact that a substantial number of pregnancies are unplanned. The committee concluded that the utility gain suggested by the company could be used as proxy for anxiety in pregnant women, and that ideally sapropterin would be offered as early as possible in the pregnancy.

### The lifelong benefits to the unborn child by reducing Phe levels in the mother could be substantial but are uncounted in the modelling

3.20 Although there are known benefits for the pregnant woman having sapropterin that were included in the cost-effectiveness analysis, there are major potential secondary and uncounted benefits to the unborn child. This potential benefit to a second individual, the unborn child, from the pregnant woman having treatment would be achieved through reducing the risk of damage in the uterus from high Phe levels (see section 3.3). During the second committee meeting, a clinical expert highlighted that sapropterin could also help pregnant women cope with the PKU diet, especially if they experience pregnancy symptoms such as morning sickness or hormone changes. Sapropterin could also allow women to tolerate more protein in their diet, which would lead to a better nutritional state and help with the growth and development of the unborn child. The ERG acknowledged that increased blood Phe levels can harm the unborn child, but the extent of lost utility is unclear, as is the effectiveness of sapropterin in reducing the risk of harm. The committee appreciated that avoiding harm to the unborn child was the reasoning behind the stricter recommended Phe levels in pregnancy. But it was not aware of any evidence to estimate the benefit to the unborn child from enhanced Phe level control or greater natural protein consumption from conception to birth. It accepted that this is challenging to model. However, it acknowledged that the risk of high Phe levels on the unborn child during pregnancy is potentially catastrophic and should be avoided if possible. It concluded that the potential lifelong benefits to the unborn child by reducing Phe levels in the mother during pregnancy could be substantial.

## Costs in the economic model

### Doses of 10 mg/kg for children and 12.5 mg/kg for adults have been assumed in the model but, if higher, would have a significant effect on the cost effectiveness of sapropterin

3.21 The company used the mean sapropterin dose for children (10 mg/kg) and adults (12.5 mg/kg) from the NHS England Integrated Impact Assessment Report to calculate the costs of sapropterin. The committee noted that because the dose is both weight-related (mg per kg of body weight), and higher in the number of mg per kg in adults than children, the total drug costs would be considerably higher for adults than children. The ERG highlighted that the proposed values may underestimate real-world dosages and costs of sapropterin and were lower than used in the PKUDOS registry. The committee concluded that any escalation above an average dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment.

### The costs of a protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain

3.22 The company estimated the costs of protein-restricted diet food and supplements based on expert advice and averaging the cost of 3 brands. It estimated costs for children under 4, children between 4 and 17, and adults, based on different rates of protein substitute and low-protein food consumption. The committee noted the high annual costs of protein-restricted diet for each group (£10,326 to £15,973). The company suggested that there would be cost savings with sapropterin, based on a 71.2% reduction in the need for low-protein foods and supplements. While the ERG considered that the total costs of protein-restricted diet calculated by the company are reasonable, it did not consider the evidence for a 71.2% reduction to be robust (see section 3.12). The ERG produced 2 scenarios with 0% and 71.2% reductions. The committee noted that sapropterin did not replace the need for diet in most people but

had been shown to be effective in combination with a protein restrictive diet in trials. Ideally this would allow people to consume more natural protein, relax the diet to a varying degree and need less low-protein food and supplements. However, the committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.

### The costs of long-term brain damage, carers' costs, carer disutilities and comorbidities associated with PKU have not been modelled

3.23 Clinical and patient experts highlighted that people with PKU are at risk of long-term brain damage if blood Phe levels are not maintained within target ranges in childhood (see section 3.1). Also, the burden of long-term brain damage in people with PKU is substantial and people are likely to have significant additional care needs (see section 3.13). However, information on long-term brain damage because of PKU is not routinely collected in the NHS. Consultation comments stated that potential long-term brain damage can also happen during adulthood (see section 3.2). The committee was also aware that high levels of Phe levels and the protein-restricted diet may contribute to comorbidities in people with PKU (see section 3.6). In addition to long-term brain damage, comments at consultation highlighted that PKU and managing the PKU diet affects the entire family and can have substantial effects on quality of life and mental health. The patients and clinical experts confirmed during the second committee meeting that both children and adults with PKU have care needs. However, they explained that the level of care varies. Children, as well as adults with disabilities or long-term brain damage caused by high Phe levels in childhood, need the highest levels. Adults are often supported by family, friends, and carers to maintain the PKU diet and deal with PKU symptoms. The committee acknowledged that comorbidities could complicate managing the PKU diet and that caregiving for people with PKU is a burden for families, parents, and partners of people with PKU. However, it had not been presented with any evidence estimating the costs of comorbidities or caregiving, or carer disutility. It concluded

that the costs of long-term brain damage after uncontrolled Phe levels in childhood, cost of potential comorbidities, and costs of caregiving and carer disutilities may be substantial and need to be considered. It also concluded that high blood Phe levels in adulthood might lead to long-term brain damage. But, the risk of new irreversible damage is considerably less than in young children and it is not known if sapropterin would prevent late effects in adults. The committee acknowledged that the costs of long-term brain damage, comorbidities, or caregiving for people with PKU are unknown and cannot be included in a model with a 1-year time horizon.

### The costs of damage to the unborn child in pregnancy may be substantial, but these have not been modelled

3.24 The effects of high Phe levels in pregnancy can be severe for the unborn child and lead to significant disability (see section 3.3). The committee noted that the effects of high Phe on the unborn child could have substantial associated NHS costs, which are not captured in the company or ERG analyses. The committee concluded that the costs of damage to the unborn child in maternal PKU syndrome may be substantial. However, these costs are unknown and are not appropriate to include in a model with a 1-year time horizon.

## Cost-effectiveness estimates

### Because of the potential uncounted benefits, an acceptable ICER is at the higher end of the range of £20,000 to £30,000 per QALY gained

3.25 The committee does not use a precise maximum acceptable cost-effectiveness level above which a technology would automatically be defined as not cost effective or below which it would. Given current limitations, NICE considers that it is most appropriate to use a range of levels, that is, below £20,000 per quality adjusted life year (QALY) gained, between £20,000 and £30,000 per QALY gained and over £30,000 per QALY gained. Additionally, consideration of the cost effectiveness of a

technology is necessary but is not the only basis for decision making. So, NICE considers technologies in relation to this range of maximum typically acceptable cost-effectiveness levels, such that the influence of other factors on the decision to recommend a technology is greater when the cost-effectiveness estimates are closer to the top of the range. Below a most plausible estimate of £20,000 per QALY gained, the decision to recommend a technology is normally based on the cost-effectiveness estimate and the acceptability of a technology as an effective use of NHS resources. Above a most plausible estimate of £20,000 per QALY gained, the committee's judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors (as relevant here):

- The degree of certainty around the cost-effectiveness estimates. In particular, the committee will be more cautious about recommending a technology when it is less certain about the estimates presented.
- Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured and may therefore misrepresent the health utility gained.
- The innovative nature of the technology.
- Aspects that relate to non-health objectives of the NHS.

As the cost-effectiveness estimate of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the committee's judgement about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed above. Above a most plausible estimate of £30,000 per QALY gained, it will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources based on the factors listed above. The committee considered that the cost-effectiveness estimates were moderately uncertain, that there were strong reasons to believe that the treatment may have benefits not captured in the modelling. No non-health objectives of the NHS were identified that have

not already been discussed in this guidance. Considering these factors and because of the potential uncounted but unquantifiable benefits in this appraisal, the committee agreed that an acceptable ICER would be towards the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

### A 10 mg/kg dose in children and 12.5 mg/kg in adults, and a 71.2% reduction in protein-restricted diet are acceptable model inputs, but both assumptions are favourable to the cost-effectiveness estimates

3.26 The company's utilities were not considered appropriate for decision making (see section 3.17). The committee expressed a preference for the ERG's approach, which focuses on the main drivers of cost effectiveness. These were: reduction in protein-restricted diet, cost of sapropterin treatment and quality-of-life benefits because of better Phe level control and reduced need for a protein-restricted diet. It was not possible to include some factors in the ERG's calculations because of the structure of the model. The most important factors are preventing permanent damage to children, young people, and unborn babies from poorly controlled Phe levels. The ERG presented 4 scenarios that differ according to combinations of 2 main assumptions: the dose (10 mg/kg for children and 12.5 mg/kg for adults, or 12.7 mg/kg for all) and the reduction in protein-restricted diet (0% or 71.2% reduction). The ICERs cannot be presented here to protect the company's confidential patient access scheme. The committee accepted that there would be some reduction in protein-restricted diet when a person was having sapropterin, but it could not be certain that it would be reduced by 71.2% (see section 3.12). However, given the lack of alternative assumptions, the committee accepted this more optimistic scenario over the 0% alternative as a basis for modelling. The scenarios also differed in dose. The committee accepted that the dose used in the PKUDOS registry would better match the efficacy estimates from the same registry (see section 3.11). Also, the assumption that the lower dose from the NHS England impact assessment report

used in the model would have the same efficacy was an assumption, and could be optimistic. The committee concluded that the ERG's scenario, using the lower dose of 10 mg/kg for children and 12.5 mg/kg for adults, and a 71.2% reduction in protein-restricted diet was acceptable. However, 71.2% may be an optimistic assumption and there was an inherent assumption that the 10 mg/kg and 12.5 mg/kg doses had the same efficacy as shown in the registry data, which could also be optimistic.

### There is no cost-effectiveness estimate presented for all ages and there are differences in the modelling for adults and children, so the age groups have been considered separately

3.27 The committee was not presented with a cost-effectiveness estimate that included all ages from the company, or the ERG. Given that different doses and different costs are used in the modelling for adults and children the committee concluded that it would consider the age groups separately.

### Sapropterin is likely to be cost effective in children under 18 assuming an average dose of 10 mg/kg

3.28 The committee considered the ERG's cost-effectiveness estimates for children under 18 in the scenario presented in section 3.25. Despite concerns about the model structure and the potentially optimistic assumption about reduction in protein-restricted diet, the committee acknowledged that there would be potential unmodelled additional benefits from sapropterin for these patients. These would particularly relate to the prevention of long-term irreversible brain damage in children, which had not been captured in the modelling and could be substantial. It noted that the ICERs for this group are likely to be within what NICE considers a cost-effective use of NHS resources, assuming an average dose of 10 mg/kg is used. In response to consultation, many comments indicated that limiting the dose to 10 mg/kg would lead to the exclusion of children whose PKU only responds to higher doses. In addition, they felt

that the dose of sapropterin should be based on individual needs and that clinicians should have flexibility in prescribing sapropterin between 5 mg/kg and 20 mg/kg according to the summary of product characteristics. During the second committee meeting, patient and clinical experts indicated that higher doses of sapropterin up to 20 mg/kg are not needed often, but flexibility in offering higher doses would be useful. Patient experts further emphasised that some children's PKU stabilises on lower doses than 10 mg/kg, while others will need higher doses. So, in practice the average dose is expected to average out at 10 mg/kg. Clinical experts explained that they would start patients with the 10 mg/kg dose but would not immediately raise it because response is not directly related to dose. In fact, one clinician advised that they would prescribe the 10 mg/kg dose to start with based on a fixed number of pills and would aim to keep the same number of pills as children grow up and their weight increases. This would be expected to decrease the dose per kg over time. One response to consultation indicated that a fixed dose approach could discriminate against children with disabilities who may be overweight because of their disability and need a consistent dose of sapropterin over time. The clinical experts confirmed that the per kg dose would apply so an overweight person would still have the higher dose they needed on a weight basis, even if limited to 10 mg/kg. One clinical expert emphasised that a robust system and criteria for determining response to sapropterin is needed because this could guide clinicians on whether they should treat PKU with sapropterin until target Phe levels are achieved or go further than this, but the committee considered this to be outside its remit. It noted that the model was highly sensitive to dosage. An analysis using an average dose of 12.7 mg/kg in children resulted in a cost-effectiveness estimate which is above the level that could be considered a cost-effective use of NHS resources, even using the higher end of the typical range. The committee agreed that the dose of sapropterin used in practice could average out, but it questioned whether there were any mechanisms in place to ensure that happens. The NHS England commissioning expert

confirmed that no such process is in place. The committee understood that for some children a dose of 10 mg/kg may not be high enough to bring their Phe levels down to reach the target levels, and a higher dose may be needed. The committee concluded that a dose of over 10 mg/kg would be justified in these circumstances based on the expectation that some children would need less than 10 mg/kg as had been stated in a consultation response. It accepted the NHS England impact assessment estimate of an average childhood dose of 10 mg/kg but noted the risk that if this dose was regularly exceeded it could then become cost ineffective for the whole child population. The committee concluded that sapropterin is likely to be cost effective in children under 18 when using an average dose of 10 mg/kg, and that it could recommend higher doses but only when this is shown to be needed to achieve acceptable Phe levels.

### Sapropterin has not been shown to be cost effective in adults with PKU

3.29 The committee noted that the both the company's cost-effectiveness analysis for adults, and the ERG's most optimistic scenario (using the adult dose of 12.5 mg/kg and a reduction in protein-restricted diet of 71.2%) resulted in ICERs for adults that were higher than could be considered a cost-effective use of NHS resources, by a very considerable margin. The committee noted that the difference in cost effectiveness in adults and children is largely driven by the drug costs (see section 3.20). This is because the sapropterin dose is based on weight. Therefore, the annual costs of sapropterin are almost 3 times higher in adults than children; but the increases in quality of life for adults do not offset these significant additional costs. Children may have more benefit because they are more likely to avoid lifelong effects of poorly controlled Phe levels, although this was not captured in the model. The committee considered the case of adults with PKU and disabilities. It acknowledged that people with PKU and disabilities have specific care needs, which can incur more costs (see section 3.6) and noted that these were not captured in the modelling. The committee was also aware of the associated comorbidities

that people with PKU may experience and that these associated costs and benefits had also not been captured in the model (see section 3.22). It was uncertain how much sapropterin alone could reduce these care needs and comorbidities. However, it agreed that any additional benefits and cost savings would not be enough to lower the very high ICERs for adults to within an acceptable range. It concluded that sapropterin is not a cost-effective use of NHS resources for adults with PKU.

### Sapropterin is not cost effective for the whole PKU population up to age 25, but it is likely to be cost effective between 18 and 21 when the same dose used under 18 is continued

3.30 Comments received at consultation indicated that stopping treatment with sapropterin would be disruptive for young adults as they transition from childhood to adulthood, and some areas of England lack of adequate adult services (see section 3.6). The committee acknowledged this and was concerned about stopping sapropterin at this difficult period for young adults. It therefore requested that the ERG do a cost-effectiveness analysis including adults aged 18 to 25 by considering children and young adults aged 0 to 25 as one group. The committee appreciated that this would involve including a subpopulation of adults for whom treatment is otherwise not cost effective, and adding this to the average childhood population where the costs were very much lower and the treatment was cost effective. The committee noted that the ICERs for this analysis were above the accepted threshold despite optimistic assumptions included in the analyses, that is,10 mg/kg dose being as effective as 12.5 mg/kg dose for adults, alongside other factors in the model that are potentially optimistic. It also gave careful consideration to potential wider benefits for young adults that are not captured in the analyses, such as risk of irreversible brain damage, need for carer or parent support, carer quality of life and successful transition into adulthood. However, it recalled that the risk of irreversible brain damage between 18 and 25 is lower than in children because the maximum benefit of keeping Phe levels low is

accrued up to 12 years of age (see sections 3.1 and 3.2). Also, the committee acknowledged that some young adults will still need carer and family support and that the PKU diet can affect carer quality of life. However, it noted that these effects are also usually lower compared with children under 18. It entirely understood the difficulties facing young adults having to transition to adult services at a sensitive time in their life and stopping sapropterin at the same time. Overall the committee considered that the additional risks in people aged 18 to 25 are lower than those for people under 18 and are not large enough to bring down the cost-effectiveness estimate into the acceptable range. However, the committee accepted that it would be beneficial if treatment could be continued for a long as possible during final brain maturation and the transition into adulthood and independence at 18. After the third meeting, the committee requested that the ERG do further analyses to explore what age above 18 sapropterin might remain a cost-effective use of NHS resources. Having reviewed this new data, the committee decided that the maximum age it could recommend treatment for was until people reach the age of 22, after which treatment became cost ineffective. These new analyses, as with the analysis up to age 25, assumed an average dose of 10 mg/kg. The committee accepted that not increasing the dose may be suboptimal for some people, but if sapropterin was escalated to the adult dose it would become cost ineffective and would have to be stopped at an earlier age. Keeping the dose the same as when the person was under 18 was considered a better choice and would allow a transition over a 4-year period to diet alone. The committee therefore concluded that sapropterin is not cost effective for the whole of the PKU population up to age 25. But, extending the treatment to age 21 is likely to be cost effective if the dose that was used under 18 is continued.

### Sapropterin is likely to be cost effective in pregnancy by reducing the risk of maternal PKU syndrome

3.31 The company had specifically addressed a subgroup of all women between 18 and 40, defined as childbearing age. As discussed in section 3.18, the company added an additional utility gain to people in this group to capture the benefit of reducing the anxiety and stress during pregnancy. However, the company's cost-effectiveness estimate for all women of childbearing age was above the accepted range considered to be a cost-effective use of NHS resources. The committee noted that the quantified benefits of sapropterin treatment would be accrued by the pregnant woman, but the benefits to the unborn child were potentially greater and were not included in the modelling (see section 3.19). It also considered whether there are any benefits to the unborn child from providing sapropterin before conception and after birth. One clinical expert explained that the mother's nutrition before conception can affect the development of the unborn child. Also, they highlighted that women with PKU give up breastfeeding because of PKU and this can affect the newborn baby's nutrition. However, the committee recalled the challenges raised during the first committee meeting in defining the optimal period of sapropterin treatment before conception and after birth. Also, it was aware that sapropterin 'should not be used during breastfeeding' according to the summary of product characteristics. Therefore, it considered that women with PKU would have to be advised to give up breastfeeding anyway if they were having sapropterin after birth. The committee noted the risk of high maternal Phe levels on the unborn child and that this can have potentially catastrophic consequences. It was also aware that pregnant women with PKU are currently offered sapropterin later than is ideal in their pregnancy under the current NHS policy and that there is an opportunity to provide sapropterin earlier. The committee noted that the effects of high Phe on the unborn child could have substantial associated NHS costs, which would be incurred throughout the child's life and are not captured in the company or ERG analyses. When taking into account the

reduction in the risk of maternal PKU syndrome and the potential lifetime benefits to the unborn child, the committee considered that these would bring the cost-effectiveness estimates below the accepted threshold. Therefore, it concluded that sapropterin is likely to be cost effective during pregnancy (from a positive pregnancy test until birth) in women with PKU.

## Equalities

### Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates

3.32 The committee understood that some people may have greater difficulty sticking to conventional dietary management of PKU and are at higher risk of being unable to control their phenylalanine levels. Some people may also have difficulty accessing healthcare services. People who face such difficulties include:

- people with a learning disability, sensory impairment, or cognitive impairment
- autistic people and people with comorbidities such as diabetes and gut disorders
- people on low incomes, with lower socioeconomic status or in insecure housing
- certain ethnic groups including people who do not speak English and Gypsy, Roma and Traveller communities
- people in social care settings
- women with PKU who need to establish controlled phenylalanine levels before conception to avoid damage to the unborn baby.

The committee considered that a positive recommendation for children and young people until they turn 22, but not for adults, was appropriate based on differing disease risk and cost-effectiveness estimates. Age is a direct indicator of greater likely benefit and lower treatment cost. Additionally, it considered that a positive recommendation for pregnant

women with PKU, but not all adults, was also appropriate based on risk to the unborn child and cost-effectiveness estimates. The committee empathised with the needs of all patients with PKU, and especially with the groups suggested above who it accepted might plausibly benefit from treatment to a somewhat greater (but unquantified) extent than the adult population at large. But, while the committee was mindful of the need to seek to reduce inequalities and advance equality of opportunity, given the high ICERs for treatment in the adult population it did not consider that any wider recommendation would be an appropriate use of NHS resources.

## Conclusion

### Sapropterin is recommended, normally at a dose of 10 mg/kg, for people under 18 with PKU for treating HPA that has been shown to respond to sapropterin

3.33 Despite the uncertainty around the assumption of reduction in protein-restricted diet (see section 3.12) and taking into account the uncaptured benefits (see section 3.26), the committee concluded that the ICER for children under 18 is likely to be within what NICE considers a cost-effective use of NHS resources. Therefore sapropterin is recommended, normally at a dose of 10 mg/kg, in people under 18 with PKU for treating hyperphenylalaninaemia (HPA) that has been shown to respond to sapropterin. A higher dose should only be used if target blood phenylalanine levels cannot be achieved at 10 mg/kg.

### Sapropterin is recommended for people with PKU aged 18 to 21, at the same dose that was used under 18, for treating HPA that has been shown to respond to sapropterin

3.34 Despite the uncertainty around the assumption of reduction in protein-restricted diet (see section 3.12) and taking into account the uncaptured benefits (see section 3.26), the committee concluded that the ICER for

young adults aged 18 to 21 is likely to be within what NICE considers a cost-effective use of NHS resources. Therefore, sapropterin is recommended in people with PKU aged 18 to 21, at the same dose that was used under 18, or at a maximum dose of 10 mg/kg, for treating HPA that has been shown to respond to sapropterin.

### Sapropterin is not recommended in adults over 21 with PKU for treating HPA that has been shown to respond to sapropterin

3.35 The costs of sapropterin are higher in adults than in children, but there is no corresponding increase in quality of life to offset these costs, and there is a lower risk of long-term brain damage in adults. Therefore, sapropterin could not be recommended for adults over 21 because it is not within what NICE considers a cost-effective use of NHS resources.

### The committee explored alternative approaches to age-based recommendations but could not find a better alternative

3.36 The committee was aware that age-based recommendations must be objectively justified, and they should be avoided when possible. It considered the justification in this case is the need to secure acceptable cost effectiveness in the interests of the NHS as a whole. Age itself is both an indicator of potentially greater benefit, coupled with lower cost of treatment. The reason for the cost-effectiveness estimates being higher in the over 18 population are explained in this guidance, as are the reasons for having 22 as the age for stopping treatment. The committee explored alternative approaches but could not find any better alternative to this approach.

### Sapropterin is recommended for pregnant women with PKU for treating HPA that has been shown to respond to sapropterin

3.37 The committee recognised that pregnant women with PKU needed to be considered differently, particularly taking into account the benefits to the unborn child. The committee concluded that the ICER for pregnant

women with PKU is likely to be within what NICE considers a cost-effective use of NHS resources. Therefore, sapropterin is recommended for pregnant women with PKU (if treatment is offered during pregnancy, that is, from positive pregnancy test until birth) for treating HPA that has been shown to respond to sapropterin. NICE is aware that a recommendation for use during pregnancy is necessarily only of benefit to people who become pregnant. This is permitted by s.17(6)(a) of the Equality Act 2010.

### Potential future generic products may allow access to sapropterin for all adults with PKU

3.38 The committee was disappointed not to have been able to extend the recommendation at least to all young adults aged up to 25, or indeed all adults. However, it was acutely aware of the lack of evidence in this disease area and the limitations of the model, which does not include several factors. It was also aware that the model has a 1-year time horizon so the long-term benefits and cost savings for people with PKU are unable to be modelled. However, even when considering these additional potential benefits of sapropterin, the price of the drug was too high to allow the ICERs to be considered an acceptable use of NHS resources. The committee was aware that generic products could be available in the near future and hoped these would be priced to allow access to this drug for all adults with PKU. This possibility has not affected the committee's consideration of sapropterin in this appraisal.

## 4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has PKU and the doctor responsible for their care thinks that sapropterin is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
August 2021

# 6 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**George Braileanu**
Technical lead

**Joanna Richardson**
Technical adviser

**Thomas Feist**
Project manager

ISBN: [to be added at publication]