NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Sapropterin for treating phenylketonuria

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sapropterin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using sapropterin in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 18 March 2021

Second appraisal committee meeting: 7 April 2021

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if:

- they are under 18
- a dose of up to 10 mg/kg is used
- 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 affects brain function in adults. The only treatment for PKU is a diet to manage phenylalanine and overall protein intake (protein-restricted diet). Sapropterin is used alongside this diet. The aim of treatment is to reduce blood phenylalanine levels and allow a less restricted diet.

Clinical trial evidence compares sapropterin alongside a protein-restricted diet with diet alone. It shows that sapropterin effectively reduces blood phenylalanine levels in people with PKU. It is uncertain how well it works because there is only short-term clinical trial evidence. There is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life.

The dose of sapropterin is based on weight so costs are higher for adults than children but there is no extra increase in quality of life for adults to offset these costs. There is also no risk of irreversible brain damage in adults with PKU. This means the cost-effectiveness estimates are higher than what NICE considers an acceptable use of NHS resources. Also, there is not enough evidence on how sapropterin might be used to prevent harm to the unborn child in women with PKU who are pregnant or trying to conceive. So, sapropterin is not recommended for adults.

When taking into account the clinical evidence and benefits that were not captured in the cost-effectiveness estimates for children, sapropterin is considered an appropriate use of NHS resources. So, it is recommended for treating PKU in children at a dose of up to 10 mg/kg.

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).

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 and reversible neurological changes in adults

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 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. 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 irreversible long-term brain damage can then mean adults have a limited ability to control blood Phe levels through 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, adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25. In adults, high Phe concentrations can result in short-term symptoms, which are considered reversible by lowering Phe levels through 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 estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels. Also, the timing, duration and intensity of exposure to high Phe levels in childhood and adolescence determine the severity of symptoms and long-term brain damage experienced by people with PKU. 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 pregnancy can have harmful effects on the unborn child

3.2 In pregnancy, high blood Phe levels can have harmful effects on the unborn child and lead to abnormal development. These effects include impaired growth, impaired learning ability and birth defects such as congenital heart defects. Clinical experts explained that maternal PKU syndrome can be worse than PKU itself because the unborn child is exposed to high Phe levels during a crucial phase of development. They noted that good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible, but there are no strict guidelines or target Phe levels used in clinical practice. The experts explained that Phe

levels should be kept low throughout the whole pregnancy. 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. However, the committee noted that about half of pregnancies are unplanned. As a result, women may be fearful of becoming pregnant, or worried that they may not be able to cope with the protein-restricted diet during pregnancy. One 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 NHS policy only covers women with PKU who are already pregnant who are unable to establish Phe levels that are not harmful to the unborn child (100 to 300 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. Clinical experts confirmed that the outcomes for pregnant women with PKU are better in the UK than other countries such as the US. But they are not ideal, and the current NHS policy is not optimal. The committee concluded that high blood Phe levels in pregnancy can have harmful effects on the unborn child. Early control of Phe levels, ideally before conception, would reduce the risks.

Treatment pathway

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

3.3 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 level. 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

3.4 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 just over 50% of adults with PKU are on a protein-restricted diet, while about 30% of adults have stopped their diet and the other 20% have difficulties maintaining it. 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.

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 carers. The committee concluded that 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 PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels

3.5 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 adequate

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 3.4). The committee understood that concerns about high blood Phe levels can also 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. 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. PKU is also 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 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. The committee concluded that there is a need for a treatment that can reduce PKU symptoms and give people with PKU and their carers peace of mind about blood Phe levels.

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

3.6 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 who have 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. The committee concluded that sapropterin is 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

3.7 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 patients having treatment with sapropterin plus protein-restricted diet significantly reduce blood Phe concentration levels and maintain target levels compared with patients having diet only. They also increase or maintain their consumption of natural Phe compared with patients 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 with protein-restricted diet is clinically effective compared with protein-restricted diet.

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

3.8 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 be responsive 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 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 patients 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 all patients enrolled in the PKUDOS registry, both those on diet alone and those taking sapropterin plus diet, would be affected by difficulties in obtaining a protein-restricted diet. It concluded that people with PKU enrolled in the PKUDOS registry were likely to reflect patients with PKU in the NHS.

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

3.9 Results from the PKUDOS registry show the proportion of patients achieving target Phe levels between 120 and 360 micromoles per litre were similar over time for all age groups. Higher proportions of patients 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 not unexpected because the target range of 120 to 360 micromoles per litre is for children under 12. The proportion of patients 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 patients 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 patients contributing long-term data at 9 years were small (between 4 and 52 patients). It also recalled that patients 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 patients achieving target Phe levels are based on Phe control with protein-restricted diet alone. Therefore, patients 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 lower than used in the PKUDOS registry and in line with European practice

3.10 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 also noted that because the dose is weight-related, the total dose and annual costs would be much higher for adults than children, over and above any difference in the dose per kg of body weight. The ERG was concerned that the doses of 10 mg/kg and 12.5 mg/kg for children and adults as 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 3.8). In the PKUDOS registry the average dose was 18.7 mg/kg and around 60% of patients were under 18 (see section 3.8). 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 was used from PKUDOS, then the dose from the PKUDOS registry should also be used, because using a lower dose may not give the same benefit. 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 patients 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 used in clinical practice in the UK would be less than that used in the PKUDOS registry and more in line with European practice.

The estimate of 71.2% reduction in protein-restricted diet is not evidence-based

3.11 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. The ERG noted 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, 1 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, all patients who have sapropterin would be expected to completely eliminate protein substitutes. The committee concluded that it seemed likely that patients would reduce their protein-restricted diet, but it could not be certain that the reduction would be as high as 71.2%.

Long-term brain damage in children is an important aspect of PKU, but there is little evidence to estimate its effect on quality of life

3.12 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 substitute (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 patients 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 is an important aspect of PKU, but there is little evidence available to estimate its effect on the quality of life of people with PKU.

The company's economic model

The model time horizon is not long enough to capture long-term brain damage and the model is not appropriate to capture the effects of PKU in pregnancy

3.13 The company used a 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) and 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 patient 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 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 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

3.14 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 descriptions should be obtained from patients and valued by the public. 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 model

3.15 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 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 symptoms 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 utility reductions to patients of all ages, despite only children being at risk of irreversible long-term brain damage because of increased blood Phe levels. Also, the ERG advised that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states (see section 3.14). 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 model.

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

3.16 The company included utility gains for all patients with mild, moderate or severe symptoms having sapropterin, in addition to the utility gain resulting from reducing PKU symptoms and protein-restricted diet. It 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 patients 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, 1 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. In addition to the unrealistically 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.

The additional utility gains modelled by the company for all women of childbearing age are not supported by evidence

3.17 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. The ERG did acknowledge that increased blood Phe levels can harm the unborn child, but the extent of lost utility is unclear, as is the effect of sapropterin on that utility loss. The patient and clinical experts further added that treatment for pregnant women with PKU could be improved, because they felt the current NHS policy meant pregnant women were having treatment too late (see section 3.2). The committee considered that the effects of uncontrolled Phe levels on the unborn child may be substantial by the time women become aware they are pregnant and then show uncontrolled Phe levels with a protein-restricted diet. It considered that the maximum benefit of

sapropterin during pregnancy would be obtained by it being available from conception. This was further complicated by the fact that a substantial number of pregnancies are unplanned. The committee noted the company included an arbitrary utility gain for all women with PKU of childbearing age. However, the benefit would be accrued by the unborn child rather than the mother, through avoiding intrauterine damage from high Phe levels. The committee was not aware of any evidence to estimate the benefit to the unborn child of enhanced Phe level control or greater natural protein consumption from conception to birth and accepted that this is challenging to model. It concluded that the additional utility gains for all women of childbearing age included by the company are not supported by evidence. However, avoiding harm to the developing fetus was clearly important, and the committee welcomes comments and further evidence on the potential use of sapropterin in women with PKU of childbearing age, or those planning pregnancy, to prevent harm to the unborn child.

Costs in the economic model

Higher doses than 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of sapropterin

3.18 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 also noted that because the dose is weight-related, the total dose and annual costs would be much higher for adults that children, over and above any difference in the dose per kg body weight. The ERG highlighted that the proposed values may underestimate real-world dosages and costs of sapropterin. The committee recalled that the sapropterin dose used in clinical practice in the UK would be less than that used in the PKUDOS registry. The committee concluded that escalation above the 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 protein-restricted diet estimated by the company are reasonable, but the cost savings with sapropterin are uncertain

3.19 The company estimated the costs of protein-restricted diet 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 3.11). The ERG produced 2 scenarios with 0% and 71.2% reductions. The committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.

The costs of long-term brain damage and damage to the unborn child in pregnancy may be substantial, but these have not been modelled

3.20 Clinical and patient experts highlighted that the burden of long-term brain damage in people with PKU is substantial and patients are likely to have significant additional care needs (see section 3.12). However, information on long-term brain damage because of PKU is not routinely collected in the NHS. The committee was aware that the effects of high Phe on the unborn child could also have substantial associated NHS costs, which are not captured in the company or ERG models. The committee concluded that the costs of long-term brain damage after uncontrolled Phe levels in childhood, and 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

A 10 mg/kg dose in children and 12.5 mg/kg in adults, and a 71.2% reduction in protein-restricted diet is acceptable

3.21 The company's utilities were not considered appropriate for decision making (see section 3.16) and the committee did not consider the company's cost-effectiveness estimates in detail any further. The ERG's model focuses on the main drivers of cost effectiveness: 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, adolescents 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 incremental cost-effectiveness ratios (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 patient was on sapropterin, but it could not be certain that it would be reduced by 71.2% (see section 3.11). However, given the lack of alternative assumptions, the committee accepted this more optimistic scenario over the 0% alternative. 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 3.10). But, it recognised that this study was done in the US where clinical practice is different, and in UK practice a lower dose would be used. Therefore, 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, even though 71.2% may be an optimistic assumption.

Sapropterin is likely to be cost effective in children under 18 only when using a dose of up to 10 mg/kg

3.22 The committee considered the ERG's cost-effectiveness estimates for children under 18 in the scenario presented in section 3.21. Despite concerns about the model structure and the potentially optimistic assumption about reduction in protein-restricted diet, the committee acknowledged that there would be additional benefits from sapropterin. These would particularly relate to the prevention of long-term irreversible brain damage in children, which had not been captured in the modelling. It concluded that the ICERs for this group are likely to be within what NICE considers a cost-effective use of NHS resources, assuming that a dose of up to 10 mg/kg is used.

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

3.23 The committee noted that the ERG's most optimistic scenario (using the dose of 12.5 mg/kg and a reduction in protein-restricted diet of 71.2%) resulted in ICERs for adults that were much higher than could be considered a cost-effective use of NHS resources. The committee noted that the company's base case for adults was also above the cost-effectiveness range. This is because the sapropterin dose is based on weight. Therefore, costs of sapropterin are much higher in adults than children; but there are no corresponding increases in quality of life to offset these costs. Also, the additional consideration of the risk of irreversible brain damage did not apply to the adult population. The committee agreed with the company and the ERG that sapropterin is not a cost-effective use of NHS resources for adults with PKU.

The committee is unable to consider women who are pregnant or planning to conceive separately, and welcomes further comment and evidence on this group

3.24 The company had specifically addressed a subgroup comprising all women between 18 and 40, defined as childbearing age. As discussed in section 3.17, the company added an additional arbitrary utility value to people in this group to capture the benefit to the unborn child. However, the company's cost-effectiveness estimate was above the accepted range. The committee noted that including all women in this age range and adding a utility value was an arbitrary approach and had not been shown to be cost effective. However, it was mindful of the importance of avoiding permanent damage to the unborn child and recalled what it had heard about current suboptimal management in the NHS. It considered that women of childbearing age or narrower populations, such as all pregnant women or those planning to conceive, should be considered further. The committee was aware that the ERG had not found any evidence to model this population separately. Therefore, the committee was unable to consider any cost-effectiveness estimates for this population. It welcomes comments and any further evidence on this subgroup.

Equalities

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

3.25 The committee understood that some people may have greater difficulty adhering to conventional dietary management of PKU and are at higher risk of being unable to control their phenylalanine. 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, living poor 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 but not adults was appropriate based on differing disease risk and cost-effectiveness estimates. However, it could not identify any specific group of adults for whom a positive recommendation could be justified given the cost-effectiveness estimates in adults. The committee welcomes any further evidence on this.

Conclusions

Sapropterin is recommended at a dose of up to 10 mg/kg in children under 18 with PKU for treating HPA that has been shown to respond to sapropterin

3.26 Despite the uncertainty around the assumption of reduction in protein-restricted diet (see section 3.11) and taking into account the uncaptured benefits (see section 3.22), 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 at a dose of up to 10 mg/kg in children under 18 with PKU for treating HPA that has been shown to respond to sapropterin.

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

3.27 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 no risk of long-term brain damage in adults. Therefore, for adults sapropterin is not within what NICE considers a cost-effective use of NHS resources. The committee recognised that pregnant women with PKU needed to be considered differently but the extent of benefits to the unborn child is unclear. The committee was unable to make a separate recommendation for this population. Therefore, it concluded that sapropterin is not recommended in adults with PKU for treating HPA that has been shown to respond to sapropterin.

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 Proposed date for 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. NICE welcomes comment on this proposed date. 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
February 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

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