Interim Clinical Commissioning Policy: Sapropterin for phenylketonuria (all ages) [200805P] (URN 1840)

Commissioning position

Summary

Sapropterin is not recommended to be available as a treatment option through routine commissioning for phenylketonuria (PKU).

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About Phenylketonuria

Phenylketonuria (PKU) is a rare genetic disorder. In this disorder, the amino acid phenylalanine (Phe) (found in food proteins) cannot be broken down and accumulates in the body. High levels of Phe are extremely toxic to the brain and untreated PKU causes profound brain damage resulting in very low intelligence quotient (IQ), seizures, muscle stiffness, autism and persistent behavioural problems. In pregnancies of women with PKU the foetus can be affected by high levels of Phe.

About current treatments

There is currently no cure for PKU. Since brain damage in PKU is caused by high levels of Phe, treatment consists of lifelong dietary management aimed at reducing Phe levels towards a safe range, using a diet which removes almost all-natural sources of protein (i.e. meat, fish, eggs, soya, nuts cheese, bread, pasta and milk). Except for fruit and some vegetables there are few foods that can be eaten freely. The diet involves calculation of daily Phe intake based on food portions and nutritional information of food labelling. Regular home blood spot monitoring of Phe levels is required to check efficacy of treatment. An artificial protein mix, with added vitamins and minerals, is taken throughout the day but patients often find this unpleasant. Keeping track of food intake requires careful planning, discipline and good reading and counting skills. As PKU impacts mood, IQ and behaviour, these patients may not have these required skills. These issues mean many adults and teenagers struggle to follow their prescribed diet, which can lead to worsening of the mood, functioning and behavioural problems caused by PKU. Successful treatment is particularly reduced in families and patients with pre-existing social vulnerabilities such as poor literacy, health literacy and poverty.

Early detection and treatment prevents severe brain damage and seizures, but even with diet treatment IQ is reduced and in adults with treated PKU there may still be poor planning and decisioning-making skills, abnormal changes on brain scans and tremors. Specialist metabolic teams conduct regular dietary reviews to avoid nutritional deficiencies and encourage dietary adherence.

There is already a published policy which covers the use of sapropterin in pregnant women: 'Sapropterin for Phenylketonuria: Use in Pregnancy' available at: https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf

About the proposed treatment

Sapropterin is a treatment taken orally once daily dissolved in water. It improves the patient's ability to process Phe, reducing or stabilising the level of Phe in the body to below or closer to the recommended levels set out in the European Guidelines, thus protecting brain function and development. The reason for using sapropterin in PKU is to sustain Phe control over time which is generally difficult to achieve with diet alone. As natural protein intake increases and reliance on synthetic protein and special low protein foods is reduced the diet becomes more manageable, thus improving dietary adherence and improving cognitive outcomes.

What we have decided

NHS England has carefully reviewed the evidence to treat PKU with sapropterin. NHS England recognises that the published evidence identifies that, at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in July 2020 for funding interventions in 2020/21, NHS England has concluded that, balanced against other relative priorities that were also considered during this process, sapropterin for PKU will not be funded at this time within the resources available.

Links and updates to other policies

This document updates the clinical commissioning policy statement E06/P/a for the use of Sapropterin in Children with Phenylketonuria.

Committee discussion

Clinical Panel noted that a NICE Technology Appraisal (TA) is underway and this guidance will determine the final commissioning position once it is published.

The Clinical Priorities Advisory Group considered the policy proposition and supporting documentation. See the committee papers (link) for full details of the evidence.

The condition

PKU is an autosomal recessive genetic disorder caused by mutations in the phenylalanine hydroxylase gene. These mutations result in deficiency of the phenylalanine hydroxylase (PAH) enzyme leading to an abnormal accumulation in the body of an amino acid called phenylalanine (Phe). The nature of the genetic mutation predicts how much enzyme is produced; some patients are completely deficient; others produce a small amount of poorly functioning enzyme. Phe is extremely toxic to the brain and untreated PKU patients have irreversible brain damage manifesting as severe intellectual disability, microcephaly, hyperactive behaviour, autistic features, seizures and behavioural problems.

This is a lifelong condition and affects both adults and children. PKU is detected in the newborn bloodspot screening programme enabling affected children to be diagnosed and start treatment soon after birth.

The effect on IQ relates to Phe exposure whilst the brain is developing and those with higher average Phe concentrations in childhood have a lower IQ. For example, Phe levels over 400 µmol/l in early childhood (therapeutic range is 120-360µmol/l) reduces IQ to 85 (Fonnesbeck et al., 2013) and another study found for each 100 µmol/L increase in blood Phe there is a predicted reduction in IQ of 1.3 to 3.1 points (Waisbren et al). In addition to absolute Phe concentration, stability of Phe levels also affects outcome and those with more variable Phe levels also suffer a greater loss of IQ (Anastasoaie et al., 2008, Hood et al., 2014, Romani et al 2019). The intended outcome of current dietary treatment includes attendance at normal school for the majority of children and an IQ within the average range. However, the outcome is dependent on the quality of blood phenylalanine control and even better-controlled patients have IQs that are 5 to 7 points lower than their unaffected siblings.

As the human brain develops until age 25 years (Steinberg, 2005, Blakemore and Choudhury, 2006), the toxic effects of elevated Phe are most marked from the neonatal period until adolescence / early adulthood. However, additional problems seen in the adult treated population include an uneven cognitive profile with low processing speed, poorer executive function, a higher incidence of attention deficits, behavioural problems, depression and anxiety, changes on brain white matter and low bone mineral density (Bilder et al 2016). These issues are more marked in patients with difficulties adhering to the diet and they have sub-optimal biochemical control. Although uncommon, some adults have developed florid neurological abnormalities such as spasticity of the legs and visual loss. These neurological impairments have improved after blood Phe has been lowered by a period of dietary treatment (Anwar et al 2013). In addition, inadequate intake of the synthetic protein substitute may result in vitamin and mineral deficiencies.

The most critical time for brain damage is at the early years when the brain is at its most vulnerable. High Phe levels are extremely damaging to a foetus, and the ‘maternal PKU syndrome’ refers to a combination of congenital cardiac defects, developmental delay, microcephaly, dysmorphic and behavioural difficulties that occur in children born to mothers with high phenylalanine levels in pregnancy. In order to prevent this syndrome women with PKU are asked to lower and maintain their phenylalanine concentration within a very tight recommended target range prior to conception and throughout pregnancy by following a prescribed PKU diet as above. Achieving this goal is challenging and clinicians consider that approximately 50% of women from UK centres currently conceive with phenylalanine concentrations greater than the recommended target range.

Current treatments

Since PKU damage is caused by high levels of Phe, treatment is aimed at lowering plasma Phe levels towards a safe range using prescribed dietary restrictions. The current treatment of PKU is by a very strict low Phe diet (10% to 20% of a normal diet). Phe is present in all natural dietary protein. A typical PKU diet therefore excludes meat, fish, cheese, milk, eggs and limits other sources of protein such as flour, pasta, rice and bread. The diet could be restricted to 3-8g protein per day which is the equivalent to the protein in 1-2 slices of bread. Protein-containing foods must be accurately measured requiring families to weigh foods. Since this restricted diet would not meet nutritional needs the diet must be supplemented with artificial amino acids, vitamins and minerals in a mixture taken 3-4 times a day. Current recommendations are that this Phe-restricted diet is continued lifelong.

Families and patients have been found to spend on average 19 hours per week on dietary compliance, thus affecting every aspect of life and testing patient’s self-control (MacDonald A et al 2016). Phe analysis is not available on packaging so dietary management requires knowledge about the relationship between protein and Phe in foods. Dietary management requires constant vigilance and control and a drastic change to usual diet and eating behaviours. Carers and patients need significant organisation and cooking skills and the ability to interpret and calculate their phenylalanine intake. In adults, neurocognitive and executive

function deficits leads to inability to sustain dietary treatment, causing chronic poor blood phenylalanine control with negative impacts on mental health, quality of life, and daily functioning.

For many PKU patients, the prescribed low Phe diet is difficult to maintain due to the limited number and type of foods (Walter 2002). The unpalatable synthetic amino acid mixtures are especially poorly tolerated and therefore adherence to dietary regimens is poor. Up to 28% of pre-school children do not attain recommended Phe targets; this figure rises to 79% of teenagers and 88% of adults (Enns et al., 2010). Given the damage that can result to the developing brain from the impact of high blood Phe, child safeguarding measures are implemented if caregivers are unable to manage the prescribed dietary treatment.

People with PKU should regularly monitor their blood Phe levels using a fingerprick test. Recommendation of frequency of monitoring varies from multiple times per week to two-four times monthly depending on age and other patient specific factors. Therapeutic targets vary with age as per the European Guidelines (van Wegberg et al., 2017). Patients with PKU are under regular follow up with specialist metabolic dieticians, to advise on dietary modification. Patients require significant support, including practical and psychosocial support.

Since current treatment with diet has suboptimal outcomes affecting the cognition, executive function and mental health of patients it is essential to consider alternative or adjunctive therapies for this condition.

There is already a published policy which covers the use of sapropterin in pregnant women with poor biochemical control: ‘Sapropterin for Phenylketonuria: Use in Pregnancy’ available at: https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf.

Proposed treatments

Sapropterin is an oral licensed product and a synthetic analogue of tetrahydrobiopterin (BH4). Tetrahydrobiopterin is a cofactor for normal function of PAH enzyme. In people with mutations that cause residual PAH enzyme activity, sapropterin stabilises the faulty enzyme and allows some PAH function to be restored.

Treatment aims to lower the blood Phe levels to close to or below the European Guideline levels (therapeutic ranges are: 120-360 µmol/l up to 12 years, 13 years onwards 120-600 µmol/l, women who are planning a pregnancy 120-360 µmol/l). Sapropterin treatment enables increased natural protein intake (Evers et al. 2018) and reduced synthetic protein requirement while maintaining lower Phe levels. For each 100 µmol/L increase in blood Phe there is a predicted reduction in IQ of 1.3 to 3.1 points (Waisbren et al. 2007), therefore the Phe lowering-impact of successful treatment with sapropterin will impact on cognitive outcomes.

Epidemiology and needs assessment

The incidence of PKU varies by population and in England it is estimated at 1 per 10,000/14,000 and the number of individuals under regular follow up is approximately 2000. The majority of individuals with PKU in England have severe mutations and therefore it is estimated that only about 25-30% of the English population are likely to respond to sapropterin. This gives an estimate of 500 eligible individuals of all ages. It is anticipated that the number who would, over time, access treatment is less than this figure, approximately 300-330. It is thought that this population is split evenly between adults and children.

Evidence summary

Clinical effectiveness

This section considers whether sapropterin is clinically effective in people with PKU who need treatment to control phenylalanine levels, compared to no sapropterin treatment.

Blood phenylalanine concentration

In a systematic review and meta-analysis of 4 RCTs by Qu et al. (2019) including 307 adults and children with PKU responsive to sapropterin, people treated with sapropterin for 3 to 6 weeks had statistically significantly lower blood phenylalanine concentrations compared with people treated with placebo or phenylalanine-restricted diet only (weighted mean difference [WMD] −100.37 micromol/litre, 95% confidence interval [CI]: −157.11 to −43.62, p=0.0005).

In a subgroup of people with lower concentrations of phenylalanine in their blood at baseline (less than 600 micromol/litre; 2 RCTs, n=101; study durations 4 weeks and 6 weeks), Qu et al. found there was no statistically significant difference between sapropterin and placebo or phenylalanine-restricted diet only over 4 to 6 weeks (WMD −7.75 micromol/litre, 95% CI −82.63 to 67.13, p=0.84). By contrast, in people with high blood phenylalanine levels at baseline (≥600 micromol/litre; 2 RCTs, n=206; study durations 3 weeks and 6 weeks), sapropterin statistically significantly reduced blood phenylalanine concentration by about 200 micromol/litre over 3 to 6 weeks (WMD −225.31 micromol/litre, 95% CI, −312.28 to −138.34, p<0.00001) compared with placebo. However, one of the studies (Muntau et al. 2017) that included people with phenylalanine blood concentrations of less than 600 micromol/litre blood at baseline was designed to look at phenylalanine tolerance and phenylalanine blood concentrations were expected to be maintained within a range; therefore, differences in blood phenylalanine concentrations were not expected.

The meta-analysis is limited by the short duration of the included studies. A prospective registry study by Longo et al. (2015) followed 504 adults and children who had taken sapropterin continuously for up to 7 years (median dose 20 mg/kg/day for a median of 4 years). After 5 years (n=48), a statistically significant 199 micromol/litre improvement in mean blood phenylalanine concentrations was seen compared with baseline (392 micromol/litre compared with 591 micromol/litre, p=0.0009). Similar results were seen at earlier yearly timepoints, and the numbers of participants in the analyses at those timepoints were higher (for example, n=333 at 1 to 2 years; 415 micromol/litre compared with 591 micromol/litre, p=0.0001).

This reviewer could not identify a published minimal clinically important difference for blood phenylalanine concentration. The summary of product characteristics (SPC) for sapropterin defines a satisfactory response to treatment as a reduction of 30% or more in blood phenylalanine concentration from baseline or attainment of target blood levels. In the RCTs included in Qu et al., participants were known to respond to sapropterin at baseline.

Blood phenylalanine concentration in recommended range

A double-blind RCT by Levy et al. (2007) involving 89 adults and children with PKU responsive to sapropterin treatment found a higher proportion of people were able to maintain their blood phenylalanine below 600 micromol/litre at 6 weeks when treated with sapropterin (22/41, 54%) compared with placebo (11/47, 23%). The statistical significance of this difference was not reported but the result suggests that, after 6 weeks, over half of people treated with sapropterin had phenylalanine levels within the recommended limits set out in the European guidelines on the management of PKU.

Stability of blood phenylalanine concentration

A small observational study in 37 adults and children (Burton et al. 2010) found that blood phenylalanine concentrations varied less when people were treated with sapropterin compared with the pre-treatment period (mean within subject variance 4.799 compared with 6.897 respectively, p=0.0017, statistically significant). The result provided is a summary estimate of individual results presented in a graph. Information regarding estimated timepoints cannot be extrapolated from the graph. It is unclear, from this study, how this improvement affects patient-orientated outcomes such as cognitive function.

Phenylalanine tolerance

In the meta-analysis by Qu et al., 2 RCTs (n=99) considered how much phenylalanine (from diet and supplements) a person with PKU could tolerate while keeping their blood phenylalanine levels within a predefined range (less than 360 micromol/litre).

The meta-analysis found that people taking sapropterin for 10 to 26 weeks could tolerate about 20 mg/kg more phenylalanine each day compared with people treated with placebo or a phenylalanine-restricted diet only (WMD 19.89 mg/kg/day, 95% CI 10.26 to 29.52, p<0.0001).

The prospective registry study by Longo et al. found that after 6 years (n=19), mean dietary phenylalanine intake increased by about 200 mg/day (from 1000 ±959 mg/day to 1197 ±667 mg/day). Similar results were seen at earlier yearly timepoints and one later yearly timepoint (n=206 at 1 year and n=5 at 6 years). No statistical analyses were reported for this outcome.

These results suggest that sapropterin may enable people with PKU to have a less restrictive diet containing more natural protein.

Protein and amino acid intake

A small case-control study in 42 adults and children (Evers et al. 2018) looked at whether people who were taking sapropterin could increase their prescribed natural protein intake and reduce their prescribed amino acid intake without their blood phenylalanine levels increasing.

The amount of protein people were advised to eat increased by 230 mg/kg/day over 5 years in the sapropterin group compared with baseline (p<0.001, statistically significant). At 5 years, natural protein intake was 280 mg/kg/day higher in the sapropterin group than in the control group (p<0.001).

The amount of amino acid supplement people were advised to eat decreased by 670 mg/kg/day over 5 years in the sapropterin group compared with baseline (p<0.001, statistically significant). At 5 years, amino acid intake was 420 mg/kg/day lower in the sapropterin group than in the control group (p=0.002, statistically significant).

These results suggest that people taking sapropterin are able to eat a less restrictive diet. Too few data were available to assess true natural protein intake; prescribed natural protein intake was assessed instead, which is easier to measure.

Safety and tolerability

This section considers whether sapropterin is safe in people with PKU who require treatment to control phenylalanine levels, compared to no sapropterin treatment.

Four of the studies included in this evidence review considered the safety of sapropterin, including the meta-analysis of 4 trials (Qu et al. 2019) and 2 long-term studies giving data for up to 7 years (Burton et al. 2011 and Longo et al. 2015). Results of the study by Levy et al. are included in the meta-analysis by Qu et al.

Between 63% and 100% of participants in individual studies reported at least one adverse event. However, many of these were not considered to be related to study treatment (between 6% and 33% of adverse events were considered sapropterin-related in individual studies). The majority of adverse events were mild or moderate in severity, and adverse events leading to withdrawal from the studies were rare.

The most frequently reported adverse events in the clinical trials included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia. The meta-analysis by Qu et al. found no statistically significant differences between sapropterin and control for any adverse events assessed (abdominal pain, diarrhoea, pyrexia, cough, vomiting, upper respiratory tract infection, headache and oropharyngeal pain).

In the European Public Assessment report (EPAR) for sapropterin the regulators concluded that sapropterin was well tolerated. The EPAR states that hypophenylalaninaemia (defined as blood

phenylalanine 26 micromol/litre or less) was more common in people treated with sapropterin compared with placebo, noting that this is an expected result with sapropterin lowering phenylalanine levels and may indicate a need to increase dietary phenylalanine or adjust the sapropterin dose.

The SPC for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in ≥1/10 people treated with sapropterin. Common adverse reactions (occurring in ≥1/100 to <1/10 people treated with sapropterin) listed in the SPC are hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

Cost effectiveness

This section considers whether sapropterin is cost-effective in people with PKU who require treatment to control phenylalanine levels, compared to no sapropterin treatment.

No studies were identified during literature searches (see search strategy for full details) that compared the cost effectiveness of sapropterin with no sapropterin treatment in people with PKU. None of the studies included in this evidence review included an outcome investigating cost effectiveness.

Benefits of treatment by subgroup

This section considers whether there is evidence for subgroups of people who demonstrate better outcomes with sapropterin therapy.

The most clearly defined subgroup of people who are more likely to benefit from sapropterin are those who are responsive to sapropterin. In the studies included in this evidence review, treatment with sapropterin was limited to people who had a positive response to a short, test course of sapropterin. The methods for determining response varied between studies, but in general, participants received a 2 to 4 week course of sapropterin and had their phenylalanine re-measured. Participants with a marked reduction in phenylalanine from baseline, normally 20-30%, were considered sapropterin responders and continued treatment with sapropterin.

Most studies included in this evidence review did not report efficacy and safety by subgroup.

Qu et al. looked at the change in blood phenylalanine concentration in subgroups of people with different blood phenylalanine concentrations at baseline. The results of these analyses suggest that people with blood phenylalanine concentrations of more than 600 micromol/litre of phenylalanine more likely to respond to sapropterin treatment over 6 weeks than people blood phenylalanine concentrations of less than 600 micromol/litre. However, one of the studies (Muntau et al. 2017) that included people with phenylalanine blood concentrations of less than 600 micromol/litre blood at baseline was designed to look at phenylalanine tolerance and phenylalanine blood concentrations were expected to be maintained within a range; therefore, differences in blood phenylalanine concentrations were not expected.

The prospective registry study by Longo et al. reported that safety and efficacy data for children aged under 4 years (n=69) were similar to results in the overall population (n=1,189).

Policy review date

This remains an interim policy whilst we await the outcome of a NICE Technology Appraisal (TA) process. The outcome of the NICE TA will supersede this policy.

Definitions

Phenylketonuria (PKU)	The disorder caused by mutations in the phenylalanine hydroxylase gene.
Phenylalanine (Phe)	An essential amino acid found in food.
Synthetic protein	Protein usually made up of essential, semi-essential and non-essential amino acids, without phenylalanine. It replaces natural protein.
Low protein special foods	Products such as flour, bread, pasta that are produced for the treatment of PKU and are available on prescription in UK. They have low protein/Phe content.
Sapropterin	Oral licensed product and a synthetic analogue of tetrahydrobiopterin (BH4). It is licensed for the treatment of PKU
Biochemical sapropterin response test	Blood phenylalanine levels should be checked before administering sapropterin and after 1 week of use at the recommended starting dose. Response to this medicinal product is determined by a decrease in blood phenylalanine. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels over a one-month period.
Null/ Null in trans genetic mutation	Genetic mutation on both copies of a gene that results in no functioning protein being produced

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