Clinical Commissioning Policy: Sapropterin (Kuvan®) For Phenylketonuria: Use in Pregnancy

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Clinical Commissioning Policy: Sapropterin (Kuvan®) For Phenylketonuria: Use In Pregnancy

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Prepared by the NHS Commissioning Board Clinical Reference Group for Inherited Metabolic Disorders

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Policy Statement
The NHS Commissioning Board (NHS CB) will commission sapropterin for phenylketonuria (PKU) in accordance with the criteria outlined in this document.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement
The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary
Phenyketonuria (PKU) is a rare genetic condition. PKU is one of a number of disorders of the chemical breakdown of amino acids, which are building blocks of protein. PKU is associated with developmental delay, learning difficulties and occasionally epilepsy and Parkinsonism. A special diet of protein free foods is effective and, if instituted soon after birth and strictly followed up to the age of at least 10 years, can prevent the adverse neurodevelopmental effects of PKU leading to the achievement of normal final IQ.

Sapropterin is a drug licensed for patients over the age of 4 years with PKU who respond to it, in conjunction with a low-protein diet. For reasons outlined in this policy the use of sapropterin needs to be targeted to those groups of patients with the greatest and most urgent clinical need and at highest risk of adverse outcomes. Sapropterin is not routinely commissioned presently. A definite priority group who will be eligible for treatment with sapropterin is the minority of pregnant women with PKU who are unable to establish adequate dietary control. The treatment of this group is of great clinical importance to prevent maternal PKU syndrome and lifetime adverse consequences to their offspring. If further robust outcomes based evidence is generated, further priority groups may be considered by the Clinical Reference group (CRG).

It is recommended that information on the outcome of treatments for these patients be collected and considered. This will be useful when this policy is reviewed.
1. Introduction

Phenylketonuria (PKU) is a rare genetic condition. PKU is one of a number of disorders of the chemical breakdown of amino acids, which are building blocks of protein. In PKU the enzyme which is affected is phenylalanine hydroxylase (PAH). This enzyme is responsible for converting the amino acid phenylalanine (Phe) into another amino acid, tyrosine. When the enzyme is deficient the Phe accumulates and is converted into phenylpyruvate and other related phenylketones. These products are detected in urine giving the disease its name.

Hence PKU is caused by deficiency in the activity of PAH leading to an accumulation of the substrate of the enzyme, Phe and a deficiency of its product, tyrosine. This is associated with developmental delay, learning difficulties and occasionally epilepsy and Parkinsonism. The degree of neurological impairment seen is directly related to Phe levels in the brain. There is a spectrum of disease severity in PKU related to the residual activity of the mutant PAH enzyme.

Phe in the blood is mostly derived from dietary protein. The aim of treatment is to lower Phe levels by restricting natural dietary protein with protein requirements met by the use of synthetic, Phe – free, amino acid mixtures which also contain all the vitamins and trace elements that are missing from a diet low in natural, high quality protein. Adequate calorie intake to meet energy requirements is provided by special protein free foods.

Such a diet is effective in controlling blood Phe levels and, if instituted in the neonatal period and strictly followed up to the age of at least 10 years, can lower Phe levels and prevent the adverse neurodevelopmental effects of PKU leading to the achievement of normal final IQ.

This can be discontinued after 10 years of age as IQ appears to be fixed and remains stable thereafter and independent of the quality of dietary control. Although there is no good evidence to suggest that high Phe levels lead to irreversible neurological damage in juveniles and adults, there is some evidence for subtle, reversible effects on neurocognition and there is an ongoing debate about the merits of remaining on diet for life. Experience in the UK indicates that many adults with PKU are leading normal lives having discontinued Phe - restricted, low protein diets.

2. Definitions

The drug sapropterin is a synthetic analogue of the molecule tetrahydrobiopterin which is a co-factor for the enzyme which is deficient in PKU. It is licensed for patients over the age of 4 years with PKU who respond to sapropterin in conjunction with a low- protein diet.
3. Aim and objectives

Clinical management and commissioning issues with regard to sapropterin are:
- For most patients diet is more effective and much cheaper than sapropterin.
- However the low protein diet is tedious and continuous compliance can be an issue.
- Also the patients who are most likely to respond to sapropterin are those with lower baseline Phe levels (≤1000µmol/L) and milder disease.
- Studies are small with potential biases from difficulty in controlling diet and with dietary fluctuations in Phe intake.
- Categories of responsiveness to sapropterin. The choice of a 30% reduction in baseline Phe levels as an indicator in research studies was arbitrary.
- Highly expensive drug – annual cost to treat an average adult for a year is £50k- 100k. In comparison the amino acid supplements and low protein foods required for dietary treatment are readily available and fully funded by most European health care systems. Their annual costs are £12k annually.
- The drug is licensed for use in children over the age of 4 years.
- Maternal PKU syndrome is well recognised in babies exposed to high levels of Phe in-utero. In maternal PKU, there are issues with compliance with diet in a small minority of patients, especially in mothers who have been off diet. For these women who cannot achieve adequate metabolic control on diet, the foetus is at significant risk of maternal PKU syndrome which has profound implications for its whole life. Very strict dietary control and the maintenance of plasma Phe levels between 100 and 300 µmol/L throughout pregnancy can prevent birth and developmental defects. Outcomes are good if women are commenced on a pre-conception diet and Phe levels are within the former range when they conceive or if the target range can be achieved within eight weeks after conception. Therefore we need to use all the tools available to us, including sapropterin, to try and obtain metabolic control in these women for the duration of pregnancy.
- Hence the use of the drug has to be targeted to those groups of patients with the greatest and most urgent clinical need and at highest risk of adverse outcomes.

4. Criteria for commissioning

**General**
- This policy applies to any patient for whom the NHS CB is the Responsible Commissioner
- Sapropterin will not be routinely commissioned.
- Priority groups who will be eligible for treatment with sapropterin are the minority of pregnant women with PKU who are unable to establish adequate dietary control and achieve the target non-teratogenic range of Phe (100-300 umol/L).
Introduction

- Maternal PKU syndrome is seen in babies of mothers with PKU and consists of a combination of cardiac and skeletal defects, microcephaly, developmental delay, prematurity and low birth weight. It can be prevented if mothers maintain strict metabolic control throughout pregnancy (Phe between 100 and 300 µmol/L). Because of this, women with PKU who are planning pregnancy are encouraged by their metabolic consultants to establish dietary control before they conceive. However if women present once they are pregnant it is important to bring Phe levels down as quickly as possible.
- In the experience of the national unit, all women can obtain the required Phe levels with appropriate dietary treatment (e.g. if admitted as an inpatient), and most manage to do this successfully at home. Some women however, for whatever reason, struggle to follow the dietary regimen and fail to get their Phe levels into target range. In these cases all possible steps should be taken to help them obtain metabolic control.

Protocol for the use of sapropterin in pregnant women with PKU whose Phe levels remain high despite dietary treatment

Preconception management

- Patients will be offered the opportunity to attend the metabolic dietetic kitchen for dietary education.
- Most women who are on normal, unrestricted diets will be expected to attend for at least two sessions, but those who have recently been on preconception or pregnancy diets, and those who habitually follow a low protein diet may not need additional dietary education.
- Patients will be established on a low protein diet and amino acid supplements.
- They will be asked to send blood spots for monitoring of Phe levels twice a week. With the help of the metabolic dieticians, women will adjust their protein intake to obtain plasma Phe levels of between 100 and 300 mc mol/l.
- Once levels have been stable within this range for at least three weeks, subjects will be advised that it is safe to start to try to conceive.

Treatment with sapropterin:

- All pregnant women who fail to establish metabolic control will be tested for sapropterin responsiveness.
- Sapropterin responsiveness testing will be done by administering sapropterin at a dose of 20 mg/kg per day for two weeks. During this time, patients will commit to continue to follow dietary advice as before and to collect blood spots three times a week.
- Response to sapropterin will be assessed by comparing Phe levels at baseline and during treatment, as before. If a response (which in this case would be any significant reduction in Phe levels as judged by the clinical team) is seen at any time during the two week testing period, the patient will continue on sapropterin.
- For the remainder of the pregnancy, a combination of sapropterin and low protein diet will be used to try to keep plasma Phe levels within, or as close as possible to, the target range of 100-300 mc mol/l. The dose of sapropterin used can range from 5-20 mg/kg/day.
In women who are not responsive to sapropterin, failure of metabolic control will be managed in the usual way. Patients are offered intensive dietary support. The dose and frequency of amino acid supplements can be increased. If necessary, patients can be admitted to hospital for direct supervision of their diet. These measures will also be available, if needed, for sapropterin responsive patients who continue to have poor metabolic control once established on sapropterin.

For patients who are taking sapropterin, the drug will be stopped immediately after delivery. All patients will return to standard management after delivery. They will be given the option to continue on a dietary treatment if they choose.

As the effects on the foetus are currently unknown the patient should be fully informed of the status and experience of this drug.

All foetal anomalies occurring in patients treated with sapropterin (regardless of the potential cause) must be reported on the Yellow Card System.

Detailed foetal anomaly scans in women who are failing to obtain adequate metabolic control will be undertaken.

Based on guidance produced by Dr Robin Lachmann PhD MRCP, Consultant in Metabolic Medicine, Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG

5. Patient pathway

Ideally patients should have been transferred from specialist paediatric metabolic services to UCLH, Addenbrooke’s Hospital, St Thomas’, Salford Royal Trust, Queen Elizabeth Hospital, Birmingham and Sheffield Teaching Hospital, when they reach 16-18y, so they are known then to adult services. They then would let the specialist metabolic team know when they want to plan for pregnancy/are pregnant. However, this doesn’t always happen and some referrals are received direct from GPs.

6. Governance arrangements

Selected hospitals (adult metabolic units) are qualified to undertake the clinical management of pregnant women with PKU:

This should be as per adult service specification for IMD. Units need physicians and specialist dietetic input. It is the regional adult metabolic unit that is responsible for metabolic control in pregnancy therefore they are responsible for metabolic control and testing for response to sapropterin and prescribing of sapropterin.

The optimal composition of the specialist regional multidisciplinary team (MDT) from pre-conceptual care to delivery

- Metabolic physician Specialist
- metabolic dietician GP
- Obstetrician Midwife
There is a need for MDTs to follow-up individuals with PKU to communicate the importance of pregnancy planning, to manage PKU pregnancies and to follow up the offspring.

**Scope, if any, for shared care**

Not from the metabolic control point of view. The way specialist units work is that women send in blood spots three times a week and their dieticians will phone them with the results and to advise on dietary care. For women who are failing metabolic control, there is an important role for local maternity services in monitoring the pregnancy with detailed foetal growth and anomaly scans, and for the local GP practice and midwife to try and make sure that regular blood spots are sent.

**The role of MDT obstetrician and selection of place of delivery**

Providing there are no concerns about the foetus (e.g. known congenital heart disease), woman can deliver locally. The role of materno-foetal medicine is to provide detailed foetal monitoring to check for growth, anomalies etc. If scans indicate major risk to foetus, then delivery could be arranged in the specialist materno-foetal medicine unit.

**Follow-up of the babies of women with maternal PKU syndrome can be by their regional metabolic unit or the lead national unit**

A neuropsychological assessment is suggested at about 18 months, then at 4-5 years, 8 years and 14 years. This will enable metabolic units to monitor cognitive outcomes and correlate them with maternal metabolic control in pregnancy, and to detect any problems early so that appropriate interventions can be put in place. These assessments are best done by a neuropsychologist attached to the metabolic centre (adult or paediatric) rather than by local child development services in gain extensive experience of the rare condition and learn to recognise the associated problems (we know that there is a high incidence of ADHD in these children). This could be done at a national centre, but that would require resource and would need patients to travel, so it may be best for each regional centre to offer the same follow-up programme for children. This be offered to all children of PKU mums, not just those who have poor control, although it is particularly important in the group we are discussing here as they will be defined at high risk of having significant neuro-developmental problems.

**7. Epidemiology and needs assessment**

Overall PKU occurs in about 1 in 15000 births with considerable variation in incidence among different populations. Prevalence of PKU in Ireland is 1 in 4000.

**8. Evidence base**

**Key Trials of Efficacy and Safety**


This phase II trial was a screening study to identify a suitable cohort of sapropterin-responsive patients. This was defined as a > 30% reduction in blood Phe levels from baseline to day 8 following daily oral treatment with sapropterin (on a dose of 10mg/kg) but on usual dietary intake. Patients were selected on the basis that their Phenylalanine (Phe) levels were ≥ 450 μ mol/L and they were not on a strict Phe diet for PKU. 490 (> 8 years of age) patients were recruited to yield 96 patients for the long-term phase III study.

The study aimed to assess the efficacy and safety of sapropterin compared to placebo, for the reduction of phenylalanine (Phe) in the blood of patients with PKU. 89 patients were screened. These patients had 1) relaxed or abandoned a strict low Phe diet and 2) previously taken part in a phase I screening study. The latter had identified them as a cohort of responders to sapropterin i.e. ≥ 30% reduction in baseline (day 1) Phe level at day 8 (after an 8 day course of daily sapropterin at 10 mg/kg).

These responsive patients were re-screened for the second study and eligibility criteria were blood Phe levels of ≥ 600 μ mol/L. Patients were then randomised 1:1 between sapropterin (10 mg/kg) and controls. The primary end-point was to measure the change in blood phenylalanine concentration from baseline to week 6 and the proportion of patients with blood Phe less than 600 μ mol/L at week 6. Patients in the treatment group were allocated to receive 10 mg/kg of sapropterin once daily for 6 weeks. 47 patients were randomly assigned to receive sapropterin and 47 to receive placebo. Treatment compliance was high (82%). Mean blood Phe at baseline was 842.7 μ mol/L for the sapropterin group and 888.3 for the controls. At 6 weeks 44% of the sapropterin group compared with 9% of controls had a blood Phe reduction of 30% or more and 32% compared with 2% had a reduction of 50% or more. The mean blood Phe fell to 619.9 from 842.7 in the treatment group (299.6 difference) but in the control group remained steady for the duration of the study.

The mean difference in both groups for change in Phe levels (baseline to week 6) was – 245 μ mol/L. At screening 17% of patients assigned to sapropterin had a blood Phe level of < 600 μ mol/L this increased to 54% at 6 weeks (compared with 19% and 23% respectively for the control group). For Phe levels < 360 μ mol/L at week 6, the proportions were 32% and 2% in the test and control groups respectively.

Summarising: 35% more patients on sapropterin (10 mg/kg) compared with controls showed a Phe drop of at least 30%. After 6 weeks of sapropterin treatment patients had a mean decrease in blood Phe level of 236 μ mol/L compared with a 3 μ mol/L increase in the placebo group. Blood Phe fell by about 200 μ mol/L after 1 week in the sapropterin group and this reduction persisted for the remaining 5 weeks of the study. It must be emphasized that this patient group had relaxed or abandoned a low Phe diet.

Patients for whom sapropterin did not reduce blood Phe might not have been BH4-responsive. The latter cannot reliably be predicted from PAH genotype and may need to be determined in response to a loading dose of 6R-BH4. A method of doing this to give 2 doses of 20 mg/kg of sapropterin 24 hours apart and measure blood Phe at 0, 4, 8, 12, 24 and 48 hours after the first dose. A reduction of 30% in blood Phe is indicative of responsiveness.


Aim of this RCT was to study the ability of sapropterin to increase Phe tolerance and reduce blood Phe concentration. In part 1, subjects with PKU and on Phe dietary restrictions were screened for sapropterin responsiveness by giving them once-daily sapropterin 20 mg/kg/d for 8 days. Patients were 4 – 12 years of age and had a mean blood Phe concentration ≤ 480 μ mol/L at screening and the same levels over the 6 months prior to study enrolment.
Responders were defined as those who achieved a ≥ 30% reduction in blood Phe between day 1 – 8 and on day 8 had a blood Phe concentration of ≤ 300 μmol/L. They were then allowed to enter Part 2 after a washout period of ≥ 1 week and were randomized (3:1) to receive a 10 week course of sapropterin, 20 mg/kg/d or placebo. Patients were instructed to maintain a stable Phe restricted diet throughout the study. Starting from week 3, Phe supplements were added or removed at fortnightly intervals based on the blood Phe concentrations from the previous week.

The primary efficacy end-point for Part 1 was the proportion of subjects classified as responders and who on day 8 had a blood Phe concentration of ≤ 300 μmol/L and a reduction in blood Phe concentration of ≥ 30%. The primary efficacy endpoint for part 2 was the daily Phe supplement tolerated by the sapropterin group at week 10, in comparison to the placebo group and the difference in blood Phe concentrations in the sapropterin group between week 0 and week 3.

Results: 90 subjects were enrolled in Part 1 of the study and 50/89 (56%) responded. 46 subjects were then randomised in Part 2 (3:1) to receive sapropterin (33 subjects) or placebo 12.

At the baseline in Part 1, mean blood Phe level over prior 6 months in the sapropterin and placebo groups was 314 and 303 respectively; baseline dietary intake at week 0 was 16.3 and 16.8 mg/kg/d and mean blood Phe < 300 (over past 6 months)) was 48% and 42% respectively.

The 50 responders in part 1 experienced a decrease in mean blood Phe from 317 on day 1 to 108 on day 8. The mean % change was 64%. There was no change in the blood Phe concentrations of non-responders.

During Part 2, over the 10 week period, the sapropterin treatment group tolerated a mean Phe supplement of 20.9 mg/kg/d compared with 2.9 mg/kg/d in the placebo group. The sapropterin group had a mean Phe level of 340 μmol/L at week 10. In the sapropterin group, total Phe intake at week 10 (dietary plus supplement) reached a significant 43.8 mg/kg/d (compared with 23.5 mg/kg/d in the placebo group), an approximate doubling in the Phe taken.

Phe supplement tolerance varied within the sapropterin group. Over the 10 week period, 12/33 (36%) in the sapropterin group tolerated an increase of Phe supplement of ≤ 10 mg/kg/d, 10/33 (30%) tolerated an increase of 11 to 30 mg/kg/d and 11 (33%) tolerated an increase of 31 to 50 mg/kg/d.

Summarising: Subjects with PKU who are responsive to sapropterin have a reduction in blood Phe levels and improved Phe tolerance. As a result they can increase their dietary Phe intake and maintain equal or better Phe control.

In this study sapropterin treatment increased Phe tolerance significantly representing an approximate doubling for the mean Phe taken and for 30% the increase reached 30 to 50 mg/kg/d (compared to 16.8 mg/kg/d at baseline), whilst still achieving prescribed blood Phe control goals of therapy.

The conclusion of the present study are restricted to children with PKU, with blood Phe concentrations controlled on a Phe-restricted diet, and who are responsive to sapropterin.

**Conclusion**

There is data from a phase II screening study and two small RCTs that sapropterin decreases blood Phe levels and increases tolerance to dietary and supplemental Phe.
There is evidence of a dose-response effect (20 mg/kg versus 10 mg/kg) as well as increased responsiveness at lower baseline Phe levels i.e. less than 600 μmol/L and in both patients on usual as well as restricted diets. Responsiveness appears to be better identified by prior screening for a blood Phe reduction of ≥ 30% rather than by targeting particular genetic mutations.

Sapropterin can lead to both statistically and clinically significant reductions in plasma Phe levels. In patients who respond, Sapropterin can also increase natural and supplemental protein intake whilst maintaining plasma Phe levels in the acceptable treatment range.

9. Rationale behind the policy statement

Covered under the section on aims and objectives.

The treatment of pregnant women with PKU or hyperphenylalaninemia is of great importance to prevent maternal PKU syndrome and lifetime sequelae to the offspring. Treatment should ideally start before conception. Increased risk is present when dietary control is not established until after the second trimester, especially with classic PKU.

Poor metabolic control in pregnancy is associated with poorer cognitive outcomes and increased behavioural difficulties in offspring. Complications include IUD, spontaneous abortion, preterm delivery, neonatal sequelae, microcephaly, CHD, intellectual or developmental disabilities, facial dysmorphism.

10. Mechanism for funding

From April 2013 the NHS CB will be responsible for commissioning in line with this policy on behalf of the population of England.

11. Audit requirements

1. Proportion of pregnant women with PKU with failed dietary metabolic control tested for sapropterin responsiveness

2. Proportion that are sapropterin responsive
   - Average levels of Phe in:
     i) women with PKU with good dietary, metabolic control who were not tested for sapropterin
     ii) women who tested positive for sapropterin responsiveness and received sapropterin
     iii) who tested negative for sapropterin responsiveness

3. Outcomes of pregnancy for all three categories of women in 2) above.
12. Documents which have informed this policy

- West Midlands Strategic Group Commissioning Policy 1: Ethical Framework to support priority setting and resource allocation within collaborative commissioning arrangements


- Department of Health, World Class Commissioning Competencies, December 2007,

- Department of Health, The NHS Constitution for England, July 2009,

- The National Prescribing Centre, Supporting rational local decision-making about medicines (and treatments), February 2009,
  - [http://www.npc.co.uk/policy/resources/handbook_complete.pdf](http://www.npc.co.uk/policy/resources/handbook_complete.pdf)

- NHS Confederation Priority Setting Series, 2008:
  - [http://www.nhsconfed.org/publications/prioritysetting/Pages/Prioritysetting.aspx](http://www.nhsconfed.org/publications/prioritysetting/Pages/Prioritysetting.aspx)

- West Midlands Specialised Commissioning Team, Background paper to the West Midlands Specialised Commissioning Group, Sapropterin in PKU, August 2010

- Children’s Act 2004:

13. Links to other policies

This policy is informed by the generic NHS CB commissioning policies covering experimental treatments and the process by which individual funding requests (IFR) are handled.

14. Date of review

A decision on when to review of this policy will be taken in April 2014
References

