

# **Clinical Commissioning Policy: Sapropterin for Phenylketonuria (all ages)**

**NHS England Reference: 170103P**



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Medical	Operations and Information	<b>Specialised Commissioning</b>
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

**Publications Gateway Reference: 07603**

<b>Document Purpose</b>	Policy
<b>Document Name</b>	Sapropterin for Phenylketonuria (all ages)
<b>Author</b>	Specialised Commissioning Team
<b>Publication Date</b>	21 December 2018
<b>Target Audience</b>	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs

**Additional Circulation List**

**Description** Not for routine commissioning

**Cross Reference****Superseded Docs**

(if applicable)

**Action Required****Timing / Deadlines**

(if applicable)

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**Document Status**

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# **Clinical Commissioning Policy: Sapropterin for Phenylketonuria (all ages)**

First published: December 2018

Effective from: 1 April 2019

**Prepared by NHS England Specialised Services Clinical Reference Group for  
Metabolic Disorders**

Published by NHS England, in electronic format only.

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## Policy Statement

NHS England will not routinely commission sapropterin for phenylketonuria in accordance with the criteria outlined in this document.

In creating this policy NHS England 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.

## 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 the disorder, a particular substance called phenylalanine (Phe) (which is found in some food proteins) cannot be broken down and accumulates in the body. Phe is extremely toxic to the brain and untreated PKU patients or those who do not follow a controlled diet have profound brain damage with a very low IQ, seizures and behavioural and social problems, other motor difficulties and autism.

### **About current treatments**

Since brain damage in PKU is caused by high levels of Phe, treatment is aimed at reducing Phe levels towards a safe range using a diet that is devoid of almost all natural sources of protein (i.e. meat, fish, eggs, soya, nuts cheese, bread, pasta and milk). Instead, a synthetic protein, with added vitamins and minerals, is taken throughout the day.

### **About the new treatment**

Sapropterin is a treatment that aims to reduce the severity of PKU, by improving the patient's ability to process Phe, reducing the level of Phe in the body. Reductions in the Phe levels allow patients more natural protein in their diet whilst protecting brain function and development. Sapropterin is taken orally.

The rationale for using sapropterin in PKU is to improve cognitive function. The diet becomes more manageable as the prescribed amount of natural protein can be increased and health outcomes are improved. Reliance on synthetic protein and special low protein foods is reduced.

### **What we have decided**

NHS England has carefully reviewed the evidence to treat phenylketonuria 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 November 2018 for funding interventions in 2019/20, NHS England has concluded that, balanced against other relative priorities that were also considered during this process, sapropterin to treat phenylketonuria will not be funded at this time within the resources available.

# 1 Introduction

Phenylketonuria (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 profound brain damage with a very low IQ, 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. Since PKU damage is caused by high levels of Phe, treatment is aimed at lowering plasma Phe levels towards a safe range using a synthetic diet. The treatment of PKU is by a very strict low Phe diet (10% to 20% of a normal diet). This consists of three main principles:

1. exclusion of high Phe foods e.g. meat, fish, eggs, cheese, bread, flour, pasta and aspartame;
2. provision of Phe requirement from weighed amounts of foods such as potatoes, peas, cauliflower and broccoli;
3. administration of a synthetic protein substitute to give 80 to 90% of protein requirements. It is also supplemented with vitamins and minerals.

The diet involves calculation of daily Phe intake from food, taking synthetic protein three to four times daily, and preparing home-made meals from specialist low protein flour. Families and patients spend on average 19 hours per week on dietary compliance.

Dietary adherence decreases with age (research indicates that up to 30% of children under the age of ten years and 80% by the age of 15 do not achieve acceptable Phe levels). The synthetic protein substitute is poorly tolerated and failure to take prescribed amounts of this can adversely affect blood Phe control and can cause brain damage. In addition, inadequate intake of the synthetic protein substitute results in vitamin and mineral deficiencies, Patients with PKU require intensive

weekly monitoring by a specialist metabolic dietician and patients must comply with regular blood testing. Patients require significant support, including practical and psychosocial support.

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. Additional problems seen in the 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. These issues are more marked in patients with difficulties adhering to the diet and have sub-optimal biochemical control. 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 therefore, women with PKU must lower their phenylalanine levels prior to conception and throughout pregnancy by following a prescribed PKU diet as above. There is a high rate of unplanned pregnancy despite patient education.

PKU is a broad term for deficiency of the phenylalanine hydroxylase enzyme. It is also referred to as PAH deficiency or hyperphenylalanin(a)emia. The specific genetic mutation predicts the severity of the condition and can predict to a large extent whether an individual will respond to sapropterin.

Since current treatment with diet has suboptimal outcomes it is essential to consider alternative or adjunctive therapies for this condition.

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. This means that the level of severity of PKU can be improved and



metabolic control is more achievable thus preventing deterioration in cognitive outcome in both adults and children allowing an increased amount (at least double) of natural protein in the diet whilst maintaining blood Phe levels within age respective target ranges. The rationale for using sapropterin in PKU is to improve biochemical control and therefore improve cognitive outcome. Sapropterin has been shown to increase the Phe tolerance of children with PKU by 20 to 30 mg/kg/day (Trefz et al 2009). In practical terms this would enable patients to tolerate foods such as ordinary bread, flour, pasta, pulses and all vegetables without measurement. This is more similar to a vegan diet, allowing a considerable easing of dietary restrictions which improves the amount of natural protein that can be eaten and health outcomes and social inclusion improved. Reliance on synthetic protein and special low protein foods is reduced.

## 2 Definitions

**Phenylketonuria (PKU)** refers to the disorder caused by mutations in the PAH gene.

**Phenylalanine (Phe)** is an essential amino acid found in food.

**Synthetic protein** is a protein usually made up of essential, semi-essential and non-essential amino acids, without phenylalanine. It replaces natural protein.

**Low protein special foods** are 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** is an oral licensed product and a synthetic analogue of tetrahydrobiopterin (BH4). It is licensed for the treatment of PKU.

## 3 Aims and Objectives

This policy proposition considered the evidence of sapropterin use compared to diet treatment in PKU.

The objectives were to:

- ensure evidence based commissioning with the aim of improving outcomes for patients with PKU, and
- identify clinical criteria for treating patients with sapropterin.

## 4 Epidemiology and Needs Assessment

The incidence of PKU varies by population and in England it is estimated at 1 per 10,000/14,000. In 2015-16, the incidence rate of positive screening tests for phenylketonuria was 0.013% (87 babies tested positive and 672,766 babies were tested). It is likely that the number of individuals under regular follow up is about 2000. Since the majority of individuals with PKU in England have severe mutations, it is estimated that only about 25-30% of the English population are likely to respond to sapropterin giving 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. Given the number of babies testing positive each year and the proportion that are likely to benefit from sapropterin, it is estimated that an additional 28 patients per annum would require treatment.

## 5 Evidence Base

This evidence review focuses on 3 double-blind randomised controlled trials (RCTs) (Levy et al. 2007, Trefz et al. 2009, Burton et al. 2015) and an open-label RCT (Muntau et al. 2017). Additional evidence is provided by 2 extension studies (Lee et al. 2008, Burton et al. 2011) and 5 observational studies (Longo et al. 2015, Aldámiz-Echevarría et al. 2015, Aldámiz-Echevarría et al. 2013, Feldmann et al. 2017, Cazzorla et al. 2014).

The disease-orientated outcomes reported in the evidence review (blood phenylalanine concentration and phenylalanine tolerance) are from high quality RCTs. Many of the patient-orientated outcomes (quality of life and neuro-cognitive function) are only reported in lower quality studies, including uncontrolled

observational studies, which have many limitations affecting their application to clinical practice.

Overall, the results of these studies suggest that sapropterin reduces blood phenylalanine concentrations and increases phenylalanine tolerance in adults and children with PKU, allowing people to increase the natural protein in their diet. The impact of sapropterin on development and day-to-day living is less clear, although these outcomes were reported in fewer studies, often of lower quality. Adverse events, while relatively common were generally mild to moderate in severity and rarely resulted in treatment being stopped.

No evidence was found to determine which sub-groups of patients are more likely to benefit from treatment with sapropterin.

All the studies assessed response to sapropterin treatment before starting the medicine, although the methods used to do this varied. In line with the marketing authorisation only people with a positive response to the one month response test were continued on sapropterin.

### **Clinical effectiveness:**

Levy et al. 2007 and Lee et al. 2008 found that people with PKU not adhering to a phenylalanine-restricted diet who were treated with sapropterin for up to 22 weeks had a statistically significant reduction in blood phenylalanine concentrations of approximately 200 micromol / litre from baseline (approximately 25% relative reduction). This reduction is significantly higher than that seen in people not treated with sapropterin who continued their current diet, whose phenylalanine levels remained constant. In Trefz et al. 2009, children whose phenylalanine levels were well controlled using a restricted diet had significantly lower phenylalanine concentrations after 3 weeks treatment with sapropterin compared with placebo (between group difference of approximately 135 micromol / litre in favour of sapropterin).

There is no published minimal clinically important difference (MCID) for phenylalanine concentration, although in Levy et al. (2007) more people in the sapropterin group had phenylalanine concentrations within limits recommended in the European guidelines on the management of PKU with a higher proportion of

people 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%) whilst on unrestricted diet.

No significant differences in physical growth parameters, including height, weight and head circumference, were observed from baseline to up to 2 years for children treated with sapropterin (Muntau et al. 2017, Longo et al. 2015, Aldámiz-Echevarría et al. 2013 and Aldámiz-Echevarría et al. 2015). There was also no significant difference in neuro-motor development from baseline to 26 weeks in children treated with sapropterin (Muntau et al. 2017). Most children in these studies had stable physical growth and neuro-motor development.

Sapropterin did not improve overall attention deficit hyperactivity disorder (ADHD) symptoms in adults and children with PKU, although some improvements in symptoms of inattention (being easily distracted or finding it hard to concentrate) were reported (Burton et al. 2015). Executive functioning (the set of processes that control behaviour) was reported in a 13-week study by Burton et al. 2015.

Sapropterin did not improve executive functioning in adults with PKU, although children treated with sapropterin showed significant improvements in some elements of executive functioning.

No significant improvements in clinician assessed global functioning were reported for adults or children with PKU (Burton et al. 2015). One study reported neuro-cognitive functioning / intelligence, finding no significant decline in IQ from baseline to 2 years in children with PKU treated with sapropterin (Longo et al. 2015).

Health-related quality of life was poorly reported, with 2 observational studies reporting conflicting results (Feldmann et al. 2017, Cazzorla et al. 2014).

### **Phenylalanine tolerance, dietary restrictions and nutrition:**

Trefz et al. 2009 and Muntau et al. 2017 reported that sapropterin for 10 or 26 weeks increased phenylalanine tolerance by 20 to 30 mg / kg / day compared with diet alone, although it's not clear from these studies whether patients would have been able to eat a normal, unrestrictive diet. There is no published MCID for phenylalanine tolerance, although a number of the low-quality, observational studies reported on

the number of participants who could adopt an unrestricted diet while taking sapropterin.

In Aldámiz-Echevarría et al. 2013, after 2 years treatment 78% of participants (28/36) taking sapropterin had an increase in phenylalanine tolerance, of whom 11 people could eat an unrestricted diet. In Aldámiz-Echevarría et al. 2015, after 12 months treatment with sapropterin 91% of participants (20/22) had an increase in phenylalanine tolerance, of which 2 people could eat an unrestricted diet. In Feldmann et al. 2017, the authors reported that treatment with sapropterin allowed participants to eat a partially or entirely normal diet, although patient numbers are not reported.

### **Safety and tolerability:**

Studies included in this review report on long-term safety data on sapropterin for up to 3 years. The summary of the product characteristics (SPC) for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in  $\geq 1/10$  people treated with sapropterin. Common adverse reactions (occurring in  $\geq 1/100$  to  $< 1/10$  people treated with sapropterin) include hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

and will meet annually and share a summary of the information gathered with commissioners and patient groups and produce a report detailing the patient outcomes.

## **6 Documents Which Have Informed this Policy**

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

This policy has also been informed by the E.S.PKU Guidelines (2018) <https://www.espku.org/projects/european-guidelines/>, and Public Health England's (2017) Data Collection and Performance Analysis Report: Newborn blood spot screening in the UK 2015/16.

## **7 Date of Review**

This document will be reviewed when information is received which indicates that the policy requires revision.

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