



Clinical Commissioning Policy: The use of Sapropterin in children with Phenylketonuria

Reference: E06/P/a

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Cross Reference	
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Contact Details for further information	jeremyglyde@nhs.net for policy issues

Document Status

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1 Executive Summary

Policy Statement

NHS England will not routinely commission Sapropterin for children with Phenylketonuria.

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

NHS England 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. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England 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 NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Phenylketonuria (PKU) is a rare genetic condition (affecting 1 in 12,600 North Western Europeans). It is caused by an enzyme deficiency leading to abnormal chemical build-up of an amino acid (a building block of protein) called phenylalanine. Untreated PKU is associated with irreversible brain damage, low IQ, seizures and behavioural problems. PKU is treated by a very limited diet devoid of almost all natural sources of protein (including meat, fish, eggs, milk, cheese, bread, and pasta) and instead a special protein replacement is administered throughout the day. Most

early treated children with good adherence to diet therapy have a good clinical outcome, achieving an IQ within the standard range and attain expected educational standards leading to independent lives as adults. Outcomes, however, are dependent on the quality of blood phenylalanine control and even well-controlled patients have IQs that are 5 to 7 points lower than their unaffected siblings. Dietary adherence is challenging and it is well established that metabolic control deteriorates with increasing age.

Sapropterin (Kuvan) is a drug licensed for patients aged 4 years and over. Up to 20% of children with PKU (mainly mild/moderate) are likely to gain benefit from it if used in combination with a more relaxed diet. There is good evidence to indicate that Sapropterin is effective in the short term and that it enables children to eat significant amounts of 'normal' foods which has many social and nutritional benefits. It also allows children to adhere to their treatment regimen as well as lessen the treatment burden on families.

2 Introduction

Phenylketonuria (PKU) is an autosomal recessive, inborn error of amino acid metabolism. It is caused by a deficiency of the hepatic enzyme, phenylalanine hydroxylase leading to accumulation of phenylalanine resulting in hyperphenylalaninaemia, low tyrosine concentrations, lower dopamine, norepinephrine, and serotonin production [Donlon 2008] and decreased protein synthesis [Christ 2013]. Without treatment most children develop profound and irreversible intellectual disability [Meli 2002], delayed speech, seizures and behavioural abnormalities. Increasing blood phenylalanine is clearly associated with decreased cognitive function with a probability of IQ less than 85 at blood phenylalanine over 400 $\mu\text{mol/L}$ [McPheeters et al 2012]. Other adverse outcomes include impaired executive function, reduced processing speed, attention problems, impaired fine motor skills and mental health concerns such as anxiety and depressive symptoms.

PKU is typically diagnosed by newborn screening at 5 days of age. There is a consensus that, for an optimal outcome, treatment should start as early as possible and that strict blood phenylalanine level control is of primary importance, particularly

during the first years of life. It is also recommended that diet is continued for life [Vockley et al 2014]. Most early treated children, who have commenced diet by 4 weeks of age fall within the broad normal range of general ability, attain expected educational standards and lead independent lives as adults [Blau et al 2010]. Outcome, however, is dependent on the quality of blood phenylalanine control [Waisbren et al 2007] and children may have subtle defects in intelligence quotient, attention, processing speed, fine motor skills, and perception and visual-spatial abilities [Janzen et al 2010]. Well-controlled patients have IQs that are 5 to 7 points lower than their unaffected siblings, although generally within the normal range of 92 to 102. Executive function (working memory, planning, organization, and inhibitory control) may be impaired [VanZutphen et al 2007; Leuzzi et al 2004]. Sustained attention and reaction time is reduced [Anjema 2011]. In adolescents results of meta-analysis indicate that any relaxation of blood phenylalanine concentrations $>600 \mu\text{mol/L}$ is associated with slower processing speed [Albrecht et al 2009]. Psychological and psychiatric disturbances may develop including anxiety related disorders (phobias/panic attacks), low level depression, attention deficit/hyperactivity, low mood, and agoraphobia [Anjema 2011].

The main stay of treatment for >60 years is a low phenylalanine diet which lowers blood phenylalanine concentrations. A low phenylalanine diet is started immediately on confirmation of diagnosis. Diet consists of a limited and controlled amount of natural protein (often less than 10g/day of natural protein and only 10-20% of the amount contained in a normal diet) derived mainly from non-animal food sources to provide essential phenylalanine requirements; with the majority of nutrient requirements being met by a phenylalanine-free source of L-amino acids with added micronutrients. Therefore, in a low phenylalanine diet, the main sources of nutrition are chemically derived, and with the exception of fruit and some vegetables there are few foods that can be eaten without severe limitation. Unsurprisingly dietary management is very difficult and provides a huge burden to families. It requires good caregiver knowledge, excellent organisation and cooking skills, and extraordinary motivation to adhere to such a restricted food intake when dietary non adherence may not bring obvious immediate ill effects to the child. Consequently overall adherence is poor, lack of adherence increases with age and failure to adhere

increases the risk of nutritional inadequacy and inadequate blood phenylalanine control.

Associations between the quality of blood phenylalanine control and behavioural problems, sustained attention and lower IQ with are well documented [Hooda et al, 2014; Jahja et al, 2014; Clancy et al, 2014; Anjema 2011, Huijbregts et al 2002]. A meta-analysis of all published literature including both phe levels and IQ measurements has documented an inverse relationship between IQ and mean blood phe levels when either the critical period of birth to 12 years or the lifetime of the individual is considered [Waisbren et al 2007].

Sapropterin (Kuvan) has been found to lower blood phenylalanine concentrations in patients with mild or moderate PKU. Several possibilities have been explored to explain the mechanism of the response to BH4 [Erlandsen et al, 2004, Pey et al, 2004, Gersting et al, 2010] and it is likely that the effect is multifactorial [Underhaug et al, 2012]. However, most of the recent work indicates that the mechanism in most BH4 responsive mutations is stabilization of a misfolded protein. Therefore, BH4 is acting as a Pharmacological chaperone.

The European Commission granted a marketing authorisation valid throughout the European Union for Sapropterin on 2 December 2008. So far, Sapropterin has rarely been used in the UK. It is accepted that it is effective in maternal phenylketonuria (see commissioning policy on Sapropterin (Sapropterin for phenylketonuria: use in pregnancy)).

3 Definitions

Tetrahydrobiopterin (BH4) is an endogenous enzyme cofactor that is essential for increasing phenylalanine hydroxylase (PAH) enzyme activity by stabilisation of the PAH tetramer.

Sapropterin dihydrochloride (Sapropterin®, Merck Serono SA Geneva, Switzerland and BioMarin, Novato, CA, USA), is the only pharmaceutical formulation of BH4 and is an approved drug for the treatment of PKU. It has been shown to lower blood

phenylalanine concentrations significantly in about 20% of patients with PKU, mainly with mild to moderate PKU. It is licensed for individuals aged 4 years and older.

4 Aims and Objectives

This aims and objectives of this policy are to set out the NHS England commissioning position for Sapropterin for children with Phenylketonuria.

5 Epidemiology and Needs Assessment

PKU affects approximately 1 in 12,600 of North Western Europeans. In the UK, with a population of 63,000,000 and 23.9% of the population ≤ 19 years of age, there are less than 2000 patients with PKU in this age category. The prevalence of PKU is highly variable, even within the same country, depending on the local population (PKU is less common in Asian and African populations) and upper-cut-off phenylalanine concentrations to diagnose PKU. The following gives information about variation in prevalence figures for PKU.

Prevalence of PKU

Population	Prevalence
Turkish [Ozalp et al. 2001]	1/4000
Irish [Loeber et al. 2008]	1/6200
Eastern Europe [Loeber et al. 2008]	1/3000 to 1/33,000
Western Europe [Loeber et al. 2008]	1/7000 to 1 in 33,000
Southern Europe [Loeber et al. 2008]	1/4000 to 1/36,000
USA [National Institutes of Health Consensus Development Panel 2000]	1/15,000
African [Hardelid et al 2008]	1/100,000

It is estimated that 20% of children (mild/moderate phenotype) with PKU may benefit from Sapropterin. That is less than 240 children in the UK and 200 children in

England. If the children under 4 years of age and over 16 years are excluded in England, it is likely that Sapropterin therapy will be beneficial and used for less than 130 children.

In successful Sapropterin responders, the diet is likely to be relaxed and the phe-free L-amino acids reduced by 50% [Singh 2010] and the use of special low protein foods decreased or stopped. It is estimated that at least 50% of these costs would be saved with Sapropterin use. It is unlikely that Sapropterin will completely replace diet in most children.

6 Evidence Base

NHS England considered the available clinical evidence as described by the Clinical Reference Group. NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the clinical case that was put to NHS England by the CRG is set out in Appendix A.

7 Rationale behind the Policy Statement

Sapropterin has been considered by NHS England who concluded that there was not sufficient evidence to support the routine commissioning of this treatment. The evidence review provided an assessment of effectiveness and safety of Sapropterin in the short term (up to 10 weeks) and could not demonstrate the benefits of treatment on nutritional status and cognitive development.

8 Criteria for Commissioning

NHS England does not routinely commission Sapropterin for children with Phenylketonuria.

9 Patient Pathway

Not applicable.

10 Governance Arrangements

Not applicable.

11 Mechanism for Funding

NHS England will not routinely fund Sapropterin for children with Phenylketonuria.

12 Audit Requirements

Not applicable

13 Documents which have informed this Policy

Not applicable

14 Links to other Policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of Review

This policy will be reviewed in March 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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Appendix A

NHS England considered the available clinical evidence as described by the Clinical Reference Group. NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the clinical case that was put to NHS England by the CRG is set out below.

“In BH4-responsive patients with PKU the strength of the evidence demonstrates that Sapropterin is effective for reducing blood phenylalanine and improving dietary phenylalanine tolerance (increased by at least 2 to 4 fold) in the short term (Level A evidence) but there is less evidence for longer term effects on cognition (Level C evidence), and for all other outcomes (C and D evidence).

In total 30 studies have evaluated the effects of BH4 in patients with PKU [Burton et al 2007, Levy 2007, Lee et al 2008, Trefz et al 2009, Burton et al 2011, Trefz et al 2001, Steinfield et al 2004, Shintaku et al 2004, Trefz et al

2005, Lambruschini et al 2005, Hennermann et al 2005, Burlina et al 2009, Trefz et al 2010, Humphrey et al 2011, Hennerman et al 2012, Keil et al 2013, Berlangier-Quintana 2005, Vernon et al 2010, Aldamiz-Echevarria et al 2013, Singh et al 2010, Thiele et al 2012, Vilasecca et al 2009, Ziesch et al 2012, Douglas et al 2013, Leuders et al 2013, Demirdas et al 2013, Gokmen-Ozel et al 2013, Feillet et al 2014, Christ et al 2014, Aldamiz-Echevarria et al 2014].

25/30 papers on BH4 and PKU were reviewed and two additional systematic reviews were also included. Five papers that were not included in the summary included small studies that did not fit the sub-headings presented (e.g. change in phe tolerance, long-term efficacy). All papers included either children <18 years of age or both children and adults. There were a total 743 subjects with BH4 responsive PKU included in the reviewed studies (although some subjects would have been enrolled in more than one study). Only five papers about pregnancy and BH4 were rejected as the results were not relevant to children. With the exception of the two systematic reviews, no other review papers were included.

The two systematic reviews have concluded that BH4 reduces phenylalanine concentrations and increases natural protein tolerance in some individuals with PKU in the short term [Cochrane data base systematic review: Somararalu et al 2012; Lindegren et al 2013]. In two randomised controlled trials and two open label extension phase 111 trials (organised by Biomarin), BH4 reduces blood phenylalanine in responsive patients (with significantly greater reductions observed in treated versus placebo groups) or it has significantly improved phenylalanine tolerance.

Longer term studies

10 studies (case reports, case series and cohort studies (from single and multi-centres) have reported a total of 214 patients on long term BH4 for a follow-up duration of ≤ 12 years [Trefz et al 2001; Steinfield et al 2004; Shintaku et al 2004; Trefz et al 2005; Lambruschini et al 2005; Hennerman et al 2005; Burlina et al 2009; Trefz et al 2010; Hennerman et al 2012; Keil et al 2013]. Normal somatic and psychomotor development is reported. Keil et al

2013, in 147 patients followed up for ≤ 12 years, reported median Phe tolerance increased 3.9 times with BH4/Sapropterin therapy, compared with dietary treatment, and median phenylalanine blood concentrations were within the therapeutic range in all patients. Compared with diet alone improvement in adherence to treatment was reported in 63.3% of patients. No severe adverse events were reported.

Effect of BH4 phenylalanine tolerance

At least 14 studies have reported a significant improvement in phenylalanine tolerance with BH4 [Belanger-Quinatana et al 2005; Vernon et al 2010; Aldámiz-Echevarría et al 2013; Singh et al 2010; Trefz et al 2009; Trefz et al 2010; Hennerman et al 2012; Keil et al 2013; Thiele et al 2012; Shintaku et al 2004; Trefz et al 2005; Lambruschini et al 2005; Hennerman et al 2005; Burlina et al 2005]. In a multi-centre, international retrospective study, a total of 94 patients (63.9%) with PKU received treatment with BH4 alone, and 53 patients (36.1%) were treated with BH4 in combination with a low phenylalanine diet. The median daily phenylalanine tolerance before BH4 or Sapropterin treatment in 38 patients with mild to classic PKU was 500 mg/d (200–800 mg/d). During BH4 therapy, phenylalanine tolerance increased significantly to 2500 mg/d (1500–3000 mg/d) [Keil et al 2013]. Most studies report a 2 to 4 fold increase in phenylalanine intake. Intake of phenylalanine-free L-amino acids [Singh et al 2010] and low protein foods [Thiele et al 2012] also significantly decrease. Additional micronutrient supplementation may be necessary [Thiele et al 2012].

Effect of BH4 on nutritional status

There is limited nutritional status data reported with Sapropterin but growth is reported to improve [Singh et al 2010].

Effect of BH4 on quality of life

Studies reporting health related quality of life with BH4 are limited and report inconsistent results [Ziesch et al 2012; Douglas et al 2013; Keil et al 2013; Dermirdas 2013].

Effect of BH4 on cognition/behaviour

Early results of the treatment of PKU patients with sapropterin indicate possible improvements in cognition/behaviour (Christ et al, 2013; White et al, 2010; Moseley et al, 2010). Further studies are needed

Ongoing studies with Sapropterin

KOGNITO

This is a Merck Serono long-term phase IV open-label, single-cohort study of the long-term neurocognitive outcomes in 4 Year-Old Children with PKU Treated with sapropterin (Kuvan®) for 7 Years.” (EMR700773-002). There is an estimated recruitment of 50 patients; recruitment started in October 2013 and the estimated study completion date is April 2022.

<http://clinicaltrials.gov/show/NCT01965912>

SIGNAL

A short term Merck Serono study (24 weeks) investigating the effect of sapropterin on the cognitive abilities in young adults (18 years to 29 years) with PKU is ongoing.

<http://clinicaltrials.gov/show/NCT01977820>

SIDE EFFECTS

Sapropterin has a good safety profile. Although several adverse effects have been reported they are mainly associated with mild symptoms. About 35% of the patients who participated in the pivotal trials experienced some form of side effect [Levy et al., 2007, Lee et al., 2008, Trefz et al., 2009, Burton et al., 2011]. In one patient, during a clinical trial, it was considered that Sapropterin might have contributed to aggravation of ulcerative colitis [Merck Serono Individual Case Safety Report – June 2014], but other severe adverse reactions are not reported. The Summary of Product Characteristics (SPC) identifies the following common effects (i.e. > 1 in 100): pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain and hypophenylalaninaemia. Allergic reactions are rare. The duration of side effects following dosing/ during continued administration is not known. The following drugs are known to interact with Sapropterin: levodopa,

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methotrexate, sildenafil, tadalafil and vardenafil. Summarise the results of the evidence review from the evidence review template's summary section".