Clinical Commissioning Policy: The Use of Sapropterin in Children

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

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Contents

Policy Statement

NHS England will commission Sapropterin for children 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.

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

Equality Statement

Throughout the production of this document, due regard has been given 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 in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Phenyketonuria (PKU) is a rare (affecting 1 in 12,600 of North Western Europeans), genetic condition. 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.

1. 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 µmol/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 µmol/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).*

This policy statement gives recommendations for the use of Sapropterin in children aged 4-16 years with PKU.

2. 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.

3. Aim and objectives

This policy aims to answer the following key clinical questions:

- What is the short and long term efficacy of Sapropterin?
- What is known about its effects on phenylalanine tolerance?
- Who should be treated with Sapropterin?
- What is the definition of a Sapropterin responder?
- How should Sapropterin loading tests be conducted?

- What is the starting dose of Sapropterin?
- Should mutation analysis be performed on PKU patients if Sapropterin is considered?
- What are the management recommendations for adapting diet with Sapropterin?
- What monitoring should be conducted with Sapropterin?
- What are the indications for withdrawal of Sapropterin

The objectives of this policy are to:

- consider the number of potential children with PKU who may respond to Sapropterin.
- the cost effectiveness of Sapropterin in PKU
- consider the clinical efficacy of Sapropterin
- identify clinical pathways for testing for Sapropterin responsiveness, and outline management strategies when Sapropterin is used as an adjunct to diet therapy.

4. 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	1/15,000

Development Panel 2000]	
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.

Cost savings to society

In a recent cross-sectional UK study on the burden of care on 106 caregivers of children with PKU, the dietary management of PKU was reported to incur a median time burden of over 19 hours per week. Twenty one per cent of caregivers reduced their working hours (median 18.5 hours/week) to care for their child, with a further 24% leaving their jobs completely. Severity of PKU did not affect the time component [Smith et al 2014]. Therefore for families with PKU there is a considerable time care burden as well as a significant loss of family earnings.

Additional evidence from the Netherlands on the burden of care on 24 caregivers of children with PKU found managing the phenylalanine-restricted diet represented an extra daily time burden of 1 hour and 24 minutes for caregivers (Eijgelshoven et al 2013).

5. Evidence base

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, Berlanger-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 that were reviewed are summarised below; 2 additional systematic reviews were also included. 5 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 5 papers about pregnancy and BH4 were rejected as the results were not relevant to children. With the exception of the 2 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.

Table 1: Overview of Randomised Controlled Trials with Sapropterin

Trial phase	Design and patients at baseline	Study objective	Main finding
Phase 111 Levy et al 2007	Randomised, double-blind, multi-centre, placebo-controlled evaluation of 10 mg/kg/day Sapropterin over 6 weeks in 89 responders to Sapropterin aged ≥8 years. (17 subjects were aged ≥8 years to ≤12years; the remaining subjects were >12years.	Primary objective: to assess sapropterin's ability to reduce blood phenylalanine in sapropterin responsive patients. Secondary objective: to assess drug safety. Inclusion criteria: subjects required a blood phenylalanine of ≥400 µmol/l (hence why subject's ≥8 years of age were recruited and subjects known to be poorly adherent with diet therapy).	Mean blood Phe (SD) changed by -236 (257) µmol/L on Sapropterin vs +3 (240) µmol/L on placebo. Drug adherence was high: 82% took the entire study drug dose. This was confirmed by a drug return count. 57% of subjects said they adhered to their diet during study period but unlike drug therapy, no objective

			measures were collected about dietary adherence. Also because the inclusion criteria of high blood phenylalanine concentrations at study entry meant subjects were already on relaxed or normal diet adherence to diet was known to be poor.
Phase 111 Trefz et al 2009	Randomized. Blinded, 10-week evaluation of Sapropterin (20 mg/kg/day) (or equivalent placebo tablets)added to phenylalanine-restricted diet, with additional Phe supplementation according to blood Phe levels in 46 responders to Sapropterin aged 4-12 years with a phenylalanine tolerance of <1000 mg/day and blood phenylalanine <480 µmol/l.	The objectives of this study were to evaluate the efficacy and safety of sapropterin by increasing dietary phenylalanine intake whilst maintaining blood phenylalanine control.	Daily dietary Phe tolerance (SD) increased from 0 to 21 (15 mg/kg on Sapropterin vs. only an additional 3(4) mg/kg on placebo (mean treatment difference 17.7 (4.5) mg/kg/day. Phenylalanine – free protein substitute requirements were reduced by two thirds. No serious adverse events were reported.

			The results of this study are limited to children who respond to sapropterin only. Adherence with drug or diet was not reported.

A therapeutic response to Sapropterin was defined as a reduction from baseline in blood Phe of at least 30%.

Phe: Phenylalanine

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 c*ommon* 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, methotrexate, sildenafil, tadalfil and vardenafil.

6. Rationale behind the policy statement

In PKU without dietary treatment most children develop profound and irreversible intellectual disability [Meli 2002], delayed speech, seizures and behaviour abnormalities. Increasing blood phenylalanine is clearly associated with decreased cognitive function with a probability of IQ less than 85 at blood phenylalanine over 400 µmol/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. Although dietary treatment is successful, due to severity of food restrictions and

unacceptable taste of protein substitute, many patients find this a difficult treatment and it is well established that diet adherence deteriorates with increasing patient age. Blood phenylalanine control is an indicator of dietary adherence. Approximately one third of patients have median/mean blood phenylalanine concentrations outside target treatment range with control deteriorating further with increasing age [Ahring et al 2011, Walter et al 2002, Crone et al 2005, Mundy et al 2002].

Associations between the quality of blood phenylalanine control and behavioral problems, sustained attention and lower IQ with are well documented [Anjema 2011, Huijbregts et al 2002].

Sapropterin is widely used throughout Europe for patients with mild and moderate PKU and considerable clinical experience has accrued. It is used commonly in Netherlands, Spain, Germany, France and Italy and in many European centres it is offered to all patients with PKU aged 4 years and over. It is already reported that 325 patients with PKU/ BH4 deficiency are included on the Kamper long term safety and outcome register [Trefz et al 2013].

Used as an adjunct to diet therapy in PKU, there is evidence to suggest that it is safe and improves blood phenylalanine concentrations, relaxes diet therapy and may improve quality of life. Long term, prospective data on neuro-cognitive outcome is still awaited.

The dietary management is particularly burdensome. This policy is formulated to identify the patients who are likely to obtain the best response from Sapropterin (i.e. at least 2-4 fold increase in dietary phenylalanine intake and attain 70% of blood phenylalanine concentrations within target range). There is a clear protocol for stopping Sapropterin if there is lack of measured benefit, adverse reactions or sustained poor control.

7. Criteria for commissioning

It is recommended that all children with PKU on dietary management aged 4-16 years are offered a Sapropterin response test, with a 30% reduction in blood phenylalanine being accepted as an adequate response following a 24 hour Sapropterin load. Sapropterin treatment shall then be offered to responders at a dose of 5-20 mg/kg/day.

NB: The 24 hour test is likely to identify the best responders but at the cost of missing a few slow responders

Indications and starting criteria

Two inclusion criteria shall be met to start Sapropterin treatment:

1. All children with blood phenylalanine concentrations with diagnostic phenylalanine levels ≥360 µmol/l on more than two occasions and requiring treatment with dietary protein (Phe) restriction.
2. A 30% reduction in blood phenylalanine during a 24 hour Sapropterin load.

Contra indications:

- Caution is advised when Sapropterin is used in patients with predisposition to convulsions. Events of convulsion and exacerbation of convulsion have been reported in these patients.

- Sapropterin shall be used with caution in patients who are receiving concomitant levodopa, as combined treatment with Sapropterin may cause increased excitability and irritability

Exclusions

- Children <4 years of age.
- Children with blood phenylalanine <360 µmol/l taking a normal diet.
- Adults

Starting criteria:

- A 30% reduction in blood phenylalanine following a 24 hour Sapropterin load is an indicator to start Sapropterin.

Minimal expected benefits from Sapropterin:

A 30% reduction of blood phenylalanine concentrations does not always equate to a good clinical response and so one of the following clinical outcomes shall be met within 6 months of starting Sapropterin:

- Either a two fold increase in phenylalanine tolerance or a minimum phenylalanine tolerance of 1000mg/daily (equivalent to 20g/daily natural protein).
- A 25% reduction in phe-free L-amino acid supplement requirements.
- 70% of blood phenylalanine concentrations within target range for age (over a 6 month period).

Stopping criteria:

There is no available literature citing experience of discontinuation of Sapropterin or suggesting indications or criteria for discontinuation of Sapropterin. Hence the following guidelines are based on clinical experience, consideration of the potential benefits and harm to the patients and also the cost to the NHS from poor adherence to Sapropterin treatment.

- Patients in whom the expected therapeutic benefits have not been achieved or are no longer achieved, as indicated by, for example - a sustained and elevated phenylalanine concentration above the recommended target range for age for 30% or greater, of all blood phenylalanine concentrations measurements over any 6 month period (not explained by demonstrated illness). This could be taken to indicate either poor individual therapeutic benefit or poor drug adherence.
- The sustained elevation of blood phenylalanine concentrations over any six month period will exclude temporary rise that could have occurred due to factors such as occasional dietary indiscretion, stress and weight loss or illness.
- Patients in whom significant adverse effects occur and are attributable to Sapropterin outweigh benefit.
- Patients who are unable to take the medication as advised for any reason.
- Patients in whom it is agreed that there has been an adverse effect on the quality of life due to the introduction of Sapropterin.
- Patients who do not comply with the treatment regime or associated diet

- Patients at the age of 17 years unless there is exceptional circumstances to support Sapropterin's use after this age.
    - PKU and concomitant disorders: such as inflammatory bowel disease, cystic fibrosis, diabetes.
    - Teenage pregnancy

N.B. Patients who have increased their natural protein intake to safe levels of protein intake and have discontinued L-amino acid supplement and yet maintain blood phenylalanine within target range for age, shall stop Sapropterin for 4 weeks. If 70% of phenylalanine concentrations are maintained within target range in the 4 week period, Sapropterin therapy shall be withdrawn.

There is no evidence to suggest that if the full dose of Sapropterin is stopped immediately (abruptly/i.e. without tapering) it is associated with adverse events.

Individual patient-physician contracts shall document agreed start and stop criteria for treatment with Sapropterin..

8. Patient pathway

Existing pathways

- Patients with PKU are diagnosed by newborn screening and are treated by the age of 14 days with a low phenylalanine diet when blood phenylalanine concentrations are consistently >360 µmol/l. The low phenylalanine diet consists of a limited and controlled amount of natural protein (often less than 10g/day of natural protein) 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.
- **Diet monitoring, diet adjustment and blood phenylalanine monitoring:** The diet is monitored by regular home blood phenylalanine monitoring (blood samples posted to hospital laboratory) according to national guidelines (MRC 1993) and dietary phenylalanine intake is titrated according to blood phenylalanine concentrations by IMD dieticians. Patients are contacted by their IMD team with blood phenylalanine results (telephone/letter) immediately and appropriate dietary changes made.
- **Patient review:** Patients are reviewed regularly by their IMD multi-disciplinary team in hospital clinics according to national guidelines (MRC 1993). Nutritional status (growth, dietary intake and nutritional biochemistry) and neuropsychological development is monitored. Patient adherence is monitored and assessed by review of blood phenylalanine control. (European PKU guidelines will be published in 2015 with recommendations for neuro-psychometric testing but this is not conducted routinely in PKU clinics).
- **Education:** Caregivers and children are given education about diet and PKU by the multi-disciplinary team within clinic reviews or by separate teaching events (according to local guidelines).

Proposed amendments to pathway with Sapropterin

The following criteria must be met

- **Pre-Sapropterin dietary work-up:** Re-establish phenylalanine tolerance prior to Sapropterin load by systematically challenging with more phenylalanine (an extra 50 mg/daily phenylalanine [equates to 1g/daily natural protein] every 4 weeks) until blood phenylalanine levels exceed target concentrations. Dietary phenylalanine intake shall be assessed by 3 day dietary records during this time.
    - **Sapropterin load:** A 24-hour Sapropterin response test using a single 20mg/kg dose of Sapropterin is recommended. Testing at baseline (0), 4, 8,12 and 24 hours is practical and would identify the vast majority of BH4 responders. Blood phenylalanine concentrations should be increased to over 500 µmol/l prior to the test and patients with PKU should increase their usual phenylalanine intake by 2 to 2.5 times for at least 4 days to ensure a blood phenylalanine concentration of >500 µmol/l. A 30% reduction in blood phenylalanine concentrations indicates responsiveness (BH4 response tests over a duration longer than 24 hours are likely to identify only a small number of so called 'late-responders' who may benefit from BH4 therapy. However, there is a loss of specificity and positive predictive value in tests over longer durations).
    - **Mutation analysis:** Mutation analysis will not preclude the need for a formal BH4 response test; it is not infallible and is not required in order to guide patient selection for BH4 responsiveness testing. There are a large number of mutations (>400) known to be associated with BH4 responsiveness. However, most patients with PKU are heterozygous i.e. the mutation in each of the 2 alleles is different, often occurring in combination with mutations of unknown significance. Hence, it is not indicated in order to guide investigation and management of PKU in the UK.
    - **Administration of Sapropterin post loading test:** As recommended in the SPC, Sapropterin shall be administered once a day at a starting dose of 10 mg/kg and the dose tailored to the patient's clinical response within the range of 5-20mg/kg/day. Dose changes shall be made in 5mg steps after a 3-month assessment of stability of measured Phe concentration after which a judgement can be made as to the effect of the dose change and would avoid unnecessary or premature dose changes.
    - Sapropterin shall be taken orally with food to increase its absorption. Sapropterin tablets may be swallowed whole or dissolved in 120-240 mL of water or apple juice. Once dissolved, Sapropterin shall be taken within 15 minutes.
    - The dose increase or decrease shall be at the discretion of the treating metabolic physician and a period of at least 3-months between dose changes shall be sufficient to reliably assess the effect of the dose change on Phe concentration.
    - The dose change shall be discussed and agreed in advance with the patient /caregiver(s)
    - Dose changes should only be made in collaboration with the metabolic dietician, Sapropterin is likely to be used mainly in conjunction with dietary management of PKU. Factors such as simultaneous uncoordinated dietary

changes, illness, irregular dietary intake and social factors may need to be resolved before dose changes of Sapropterin are made.

There is no evidence for the safety and efficacy of Sapropterin at doses above 20mg/kg/day.

Dietary recommendations with Sapropterin:

- **Adjusting the low-phenylalanine diet post Sapropterin:** Any increase in dietary intake must be carefully titrated with measurement of blood phenylalanine concentrations and adjustment of the sapropterin dose, where appropriate.
- **Phenylalanine intake shall be increased** by 100 mg/day (2g/day natural protein) in combination with regular monitoring of blood phenylalanine concentrations. Dietary phenylalanine shall continue to be increased, systematically, by the same amount (i.e. 100 mg/day) at 14 day intervals, but only until blood phenylalanine concentrations start to escalate beyond target blood phenylalanine concentrations. In order to establish accurate phenylalanine tolerance, any additional dietary phenylalanine shall only be introduced under stable conditions. Careful dietary records shall be kept during the dietary phenylalanine introduction phase.
- **Source of dietary phenylalanine during the introduction phase:** introduce moderate protein food sources first (containing 5-10g/100g protein) until protein tolerance is established. Foods containing >10g/100g protein shall then be cautiously introduced.
- **Phenylalanine-free L-amino acid supplement adjustment:** Two criteria shall be met before there is any reduction in the dosage: (a) the total protein equivalent intake (from natural sources and protein substitute) should supply, as a minimum, the safe level of protein intake defined by the World Health Organization [WHO/FAO/UNU 2010]; (b) all vitamin and mineral requirements should be met. Only a minority of patients with PKU are able to stop their source of protein substitute with Sapropterin, but most should be able to reduce overall dosage.
- **Monitoring:** Blood phenylalanine and tyrosine concentrations shall be monitored weekly during any dietary manipulations due to the highly variable responses to Sapropterin (this is likely to be for 3-6 months). Once stability in blood phenylalanine concentrations and dietary phenylalanine tolerance is achieved, blood phenylalanine monitoring shall be carried out according to local guidelines.
- **Other monitoring with Sapropterin:** Annual nutritional biochemistry (Vitamin B12, D, B6, zinc, iron, selenium, FBC) shall be performed.

  Long term post-marketing surveillance by means of manufacturer /NSPKU sponsored PKU registry, neuro-psychological assessment and long-term quality of life measures will be required and shall be made a requirement of the manufacturer for monitoring the safety and efficacy of Sapropterin in the UK.
- **Illness management:** Blood phenylalanine typically increase in catabolic stress (e.g. fever, trauma), and increased blood phenylalanine has been reported in febrile Sapropterin -treated or diet-treated patients with PKU [Belanger-Quintana et al 2005, Hennermann et al 2005, Trefz et al 2005]. With Sapropterin, it shall

be necessary to give the original dose of protein substitute or to reduce dietary phenylalanine intake temporarily [Trefz et al 2005, Lee et al 2008].

Annual patient monitoring to review therapeutic benefit from Sapropterin

- All patients treated with Sapropterin will be assessed annually by the treating IMD multi-disciplinary team to ensure the following criteria are being met: 1) minimal expected patient benefits; 2) no evidence of severe adverse drug effects and 3) good adherence with drug administration. If there is evidence to suggest that one or more of these criteria are not met, the drug should be discontinued immediately.

If any patient achieves safe levels of natural protein intake (WHO/FAO/UNU 2007) and discontinues phenylalanine-free amino acid supplement, then Sapropterin therapy should be stopped for 4 weeks. Blood phenylalanine levels should be monitored at least weekly and if 70% of phenylalanine concentrations are maintained within target range in the 4 week period, Sapropterin therapy shall be withdrawn.

9. Governance arrangements

All patients undertaking Sapropterin loading tests and treatment shall be under the management of a specialist IMD centre as defined in the paediatric commissioning specification for IMD.

10. Mechanism for funding

NHS England will be responsible for commissioning services in line with this policy on behalf of the population of England.

11. Audit requirements

- All patients prescribed Sapropterin will be reviewed annually to ensure they are still receiving the expected therapeutic benefits from the drug.
- The benefits of Sapropterin to the population of PKU patients in the UK and to the NHS shall be reviewed every 5 years
- All patients shall be included in the KAMPER registry. This is a European register collection long term data on the safety and outcome of patients on Sapropterin

12. Documents which have informed this policy

- NHS England. Putting Patients First. The NHS Business Plan for 2013-2015/6.
- NHS England. The Controlled Drugs (Supervision of management and use) regulations 2013 Single Operating Model Superceded.
- Department of Health, World Class Commissioning Competencies,

December 2007, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicy AndGuidance/DH_080958.

- Department of Health, The NHS Constitution for England, July 2009, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicy AndGuidance/DH_093419.
- 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.
- NHS Confederation Priority Setting Series, 2008 http://www.nhsconfed.org/publications/prioritysetting/Pages/Prioritysetting.aspx
- Children's Act 2004: http://www.opsi.gov.uk/acts/acts2004/ukpga_20040031_en_3.
- NHS Commissioning Board. NHS Commissioning Policy. Sapropterin (Sapropterin for Phenylketonuria: Use in Pregnancy. April 2013. Reference: NHSB/E12/pla.
- The NHS Constitution.

13. 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).

14. Date of review

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

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