NICE National Institute for Health and Care Excellence

# Sapropterin for treating phenylketonuria [ID1475]

## Lead team presentation

**Lead team:** Richard Ballerand, Stephen Sharp

**Chair**: Jane Adam

**ERG**: Liverpool Reviews & Implementation Group

**Technical team**: George Braileanu, Joanna Richardson, Janet Robertson

**Company**: BioMarin

2nd February 2021 – virtual meeting

# Key issues – clinical effectiveness

- Are there differences in risk between children and adults with this disease?
- Are the dietary requirements the same for children and adults?
- Is the PKUDOS registry appropriate to provide a comparison of sapropterin plus protein-restricted diet versus protein-restricted diet alone?
- Are the participants in the PKUDOS and KAMPER registries likely to be reflective of patients in the NHS?
- Are the results of the PKUDOS registry generalisable to patients in the NHS?
- What is the dose of sapropterin used in clinical practice?
- Does sapropterin allow patients to reduce their protein-restricted diet?
  - What percentage reduction in protein-restricted diet is expected after sapropterin treatment?

# Phenylketonuria (PKU) (1)

*PKU is associated with reduced phenylalanine hydroxylase activity and high blood Phe levels*

**PAH gene mutations**

PKU (or phenylalanine hydroxylase [PAH] deficiency) is a rare, inherited disorder cause by mutations in the PAH gene.

**Impaired Phe metabolism**

Mutations of the PAH gene result in decreased activity to complete inactivation of the PAH enzyme, which is responsible for breaking down phenylalanine (Phe) to tyrosine.

**Increased blood Phe**

The reduced activity of PAH means that people with PKU are unable to break down Phe, resulting in increased levels of Phe in the blood.

**Neurological damage**

- **Irreversible** and long-term in **children**
- **Reversible** and short-term in **adults**

**About 1 in 10,000 babies are diagnosed with PKU in the UK.**

**There are about 2,000 people with PKU in England.**

# Phenylketonuria (PKU) (2)

*High blood Phe levels can lead to neurological damage*

**High blood Phe concentration levels can result in neurological damage, which may be irreversible depending on the stage of brain development.**

## Children

- **Irreversible neurological damage** (early years - most critical time period for brain development)
- Can lead to **long-term disability** such as severe intellectual disability, microcephaly, seizures and tremors, stunted growth, delayed speech and impaired executive function.

## Adults

- **Reversible neurological damage** (due to compromised white matter in the brain)
- Can lead to **short-term symptoms** such as impaired executive function (attention deficits, reduced response inhibition), neuropsychiatric symptoms (depression, anxiety and inattention) and psychosocial impairments (reduced autonomy, impaired social maturity and difficulty forming relationships).

## Pregnancy

- **Teratogenic** (abnormal development) effects
- Can lead to impaired growth, impaired intellectual ability and birth defects (e.g. congenital heart defects) to the unborn child.

NICE

# Treatment pathway (1)

*Only option available for people with PKU is protein-restricted diet*

**New born screening for PKU**

(carried out within 5 days of birth through the newborn blood spot screening programme)

**Multidisciplinary team** including consultants, specialist nurses, dietitians and psychologists.

People with PKU are followed up in specialist metabolic centres according to European guidelines:

- **0–1 years:** 6 outpatient visits per year
- **>1 year:** 2–3 outpatient visits per year

**Life-long protein-restricted diet** consisting of:

- restricted natural protein intake (according to individual Phe-tolerance)
- prescribed low-protein and Phe-free medical foods → *to help reduce dietary Phe intake*
- Phe-free amino acid supplements → *to improve nutrition and prevent nutritional deficiencies*

**Routine monitoring** involving home blood samples sent to central laboratory

**Telephone consultations** to provide blood Phe concentration level results and advice on adjusting diet to manage blood Phe concentration level (if necessary)

As part of a **protein-restricted diet**, people with PKU must:

- avoid high protein foods rich in Phe (e.g. meat, fish, dairy products and soya)
- tightly control intake of foods with less natural protein (e.g. fruit, vegetables, cereals and flour)
- avoid food and drinks containing aspartame (which is converted to Phe)
- avoid alcoholic beverages containing protein (e.g. beer and stout).

# Treatment pathway (2)

- The primary aim of clinical management and protein-restricted diet is to prevent neurological damage by keeping blood Phe concentration levels within the ranges recommended in the European guidelines.

| Age | Untreated blood Phe concentration level (µmol/L) | Duration of treatment | Target blood Phe concentration levels (µmol/L) |
|---|---|---|---|
| **≤12 years** | 360 to 600 | Up to 12 years | 120 to 360 |
| **≤12 years** | >600 | Up to 18 years | 120 to 600 |
| **>12 years** | >600 | Life-long | 120 to 600 |
| **Pregnant women** | >360 | Preconception onwards | 120 to 360 |

- However, adherence and acceptance of protein-restricted diet is hindered by several factors (ERG clinical expert and clinical experts at technical engagement):
  - Complexity of food preparation which can be demanding and time-consuming for people with PKU, their carers and healthcare professionals who support and guide them
  - Poor palatability, disagreeable smell and textures of synthetic protein substitutes and amino acid mixtures which have to be taken in high volume (at least 3 times a day).

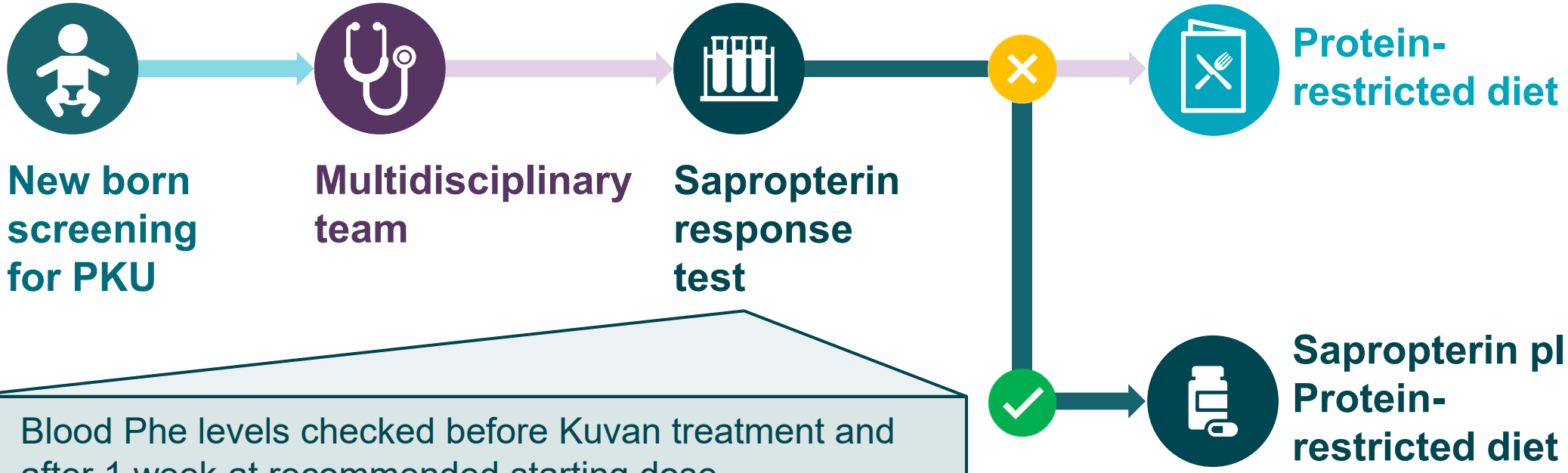
# Sapropterin (Kuvan, BioMarin)

| | |
|---|---|
| **Marketing authorisation (Dec 2008)** | "*Kuvan is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU)* ***who have been shown to be responsive to such treatment***" |
| **Administration and dose** | Recommended starting dose (children and adults): 10 mg/kg body weight once daily orally<br>• Dose adjusted between 5 and 20 mg/kg per day to achieve and maintain adequate blood phenylalanine levels. |
| **Price** | **List price:** £597.22 for 30 x 100 mg tablets<br>**Cost per patient per year** (based on list price):<br>• Children: £21,799 (weight 30 kg, sapropterin dose: 10 mg/kg/day)<br>• Adults: £65,396 (weight 75 kg, sapropterin dose: 12.5 mg/kg/day)<br>Company has agreed a confidential **simple discount patient access scheme** with NHS England |
| **Population eligible for sapropterin** | **391** people with PKU in England and Wales<br>• 366 current patients + 25 new patients each year |

Sapropterin is currently commissioned by NHS England for pregnant women with PKU who are unable to establish adequate dietary control and achieve the target non-teratogenic range of Phe (100 µmol/L to 300 µmol/L).

# Sapropterin positioning

*Company positions sapropterin as adjunct to protein-restricted diet*




- Blood Phe levels checked before Kuvan treatment and after 1 week at recommended starting dose.
- If unsatisfactory blood Phe reduction, dose can be increased weekly to 20 mg/kg/day, with continued weekly blood Phe monitoring for one month.
- Dietary Phe intake should be maintained at constant level.
- *"satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician."*

Mutation analysis can also be done to determine sapropterin response (not routine practice in the UK).

Protein substitutes are unlikely to be removed entirely to allow for some buffer and to ensure patients do not forget the taste or technique associated with protein substitute intake should they need additional protein in times of illness.

# Patient and carer perspectives (1)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Living with PKU – adults

- Adults with PKU find it difficult to juggle work, studies and/or family commitments with controlling their diet and maintaining Phe levels because of the complex and time-consuming nature of the diet. Some are unable to engage in full-time work because that creates a vicious cycle of less time to control diet and higher Phe levels leading to reduced ability to focus and organise the diet.
- In addition, they have a sense of being dependent on other people for support, feel socially isolated and constantly worry about the availability and cost food all the while dealing with the complex health issues of PKU and its effects on mental health.
    - *"I eat the same things day in day out and cannot fully engage socially as it usually revolves around food."*
    - *"I am frequently fatigued, have headaches, can't think clearly, have mood swings, tremors and I deal with depression and anxiety as a consequence."*
    - *"All 'free from' food that is also low in protein is ridiculously expensive and vegan food always has protein supplements."*
- Some adults with PKU are uncertain about the level of support that can be obtained through the healthcare system if at all. There is also confusion whether patients should come off diet altogether after a certain age.

# Patient and carer perspectives (2)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Living with PKU – adults

- Many adults describe the impact of high phenylalanine levels as *"brain fog"*, forgetfulness and feelings of irritability, which can affect their ability to control their diet and lead to a vicious cycle of high phenylalanine levels.
    - *"I have mood swings, extremely tired and want to sleep all the time and feels like this is a grey cloud hanging over my head, but not depression."*
    - *"As an adult who came off diet in my teens, I am noticing the effects of phenylalanine on my brain. I suffer anxiety, forgetfulness, fogginess, fatigue, confusion, severe depression and struggle with organisation and concentration. I have been trying to get my levels back down for a good couple of years now and I'm really struggling."*
- PKU also impacts women's sexual and reproductive health. Fear of maternal PKU can affect women's sexual and reproductive choice. Phenylalanine is highly teratogenic to the fetus and this means women with PKU are advised to have very tightly controlled phenylalanine before conception.
    - *"Pregnancy is a scary thought. There is nothing I want more than to be a mum, but I am so scared about becoming pregnant and hurting my child or myself that I have never had sex as I'm so scared of there being an accident."*
- Mothers with PKU describe being unable to cope with the pressures of strict dietary management while caring for their child; and experiencing anxiety, depression and inability to focus as a result.

# Patient and carer perspectives (3)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Living with PKU – children

- PKU is very limiting for children, who face isolation and feel restricted in their ability to join social events such as school trips, festivities, travels or meals out because of their diet.
- Children with PKU frequently experience difficulty with focus, depression or anxiety, disordered eating, digestive problems, headaches, low mood and sadness, feeling tired all the time and being in a heightened emotional state (including aggressiveness, psychosis and paranoia) as a result of high phenylalanine levels.
    - *"Within a year of being off diet… my son became feared for his safety; he believed he was going to be robbed, kidnapped or blown up. His paranoia was so extreme that he was urgently referred to a mental health unit where he was assessed as having psychosis and placed on anti-psychotic medication."*
- Teenagers with PKU also feel hungry during their growth spurt because their PKU diet does not fill them up.
    - *"My daughter was watching a nature programme where a lion was lying dying because there was no food. She started to cry and told me that was how she felt every day."*
    - *"My son is nearly 13 and going through a growth spurt... he is always hungry! The PKU diet just doesn't fill him up."*

# Patient and carer perspectives (4)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Experience of current treatment

- The low phenylalanine diet involves removing almost all natural protein from the diet. It is common for people with PKU to eat only tiny amounts of natural protein each day – equivalent to protein in 1 or 2 bread slices.
- Managing the diet is dominant activity of daily life and places great burden on individuals, parents and carers who devote extraordinary levels of time and skill to organise, prepare and cook food. Patients typically prepare special meals from prescribed low phenylalanine ingredients. They need to learn the phenylalanine content of different foods, be able to read labels, calculate and weigh out the exact amount of different foods that may be eaten.
    - *"I am finding it extremely difficult to get back on diet and stick to it. It is extremely time consuming, tiring and confusing. I feel that if I could get back on diet properly then it would all become easier, but it is so complicated. When I have a high or a low protein day I am affected for days following, this knock-on effect wears me out."*
- Low phenylalanine foods consist of prescribed wheat starch (similar to cornflour) which can be made into bread and other recipes like "burgers", "sausages" or "omelette". However, people with PKU (children especially) find these "food" unappetising or unpalatable leading to a lack of adherence to diet or daily battles for parents to get their children to stick to diet.
- There are difficulties accessing prescription food, while some doctors refuse many low protein prescription requests because they consider them as luxury items e.g. biscuits.

# Patient and carer perspectives (5)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Caring for children with PKU

- Most parents and carers of children with PKU are faced with constant pressure of dealing with dietary management and daily caring struggles as a result of:
  - Having to give amino acid supplements: *"At times for weeks sometimes months it feels we are force feeding her a drink she hates 3 times a day. A drink that at times makes her physically sick."*
  - Process of checking food labels, purchasing ingredients and preparing meals, which can take 2-3 times longer than normal: *"Staying up till 2am sometimes preparing food ahead of time to last the next few days. Checking every single food label for hidden dangers such as aspartame."*
  - Costly foods and ingredients: *"Food shopping journeys can take 2-3 times longer than they used to before PKU, with visits to multiple outlets (often buying more expensive food ranges) to attempt to broaden and vary the diet as much as possible."*
  - Dealing with children's mental health issues from anxiety and stress to depression (with no or delayed access to psychologists, despite a multidisciplinary team involved in PKU management)
  - Organising blood checks, healthcare appointments, prescription collection and deliveries: *"You do blood checks regularly and wait on some cases for 3–5 days before you get the result."*
  - Feelings of stress and fear for child's well-being, particularly the prospect of irreversible brain damage: "*When you can cause irreversible brain damage to your child, it causes a lot of worry, stress and even panic*."

# Patient and carer perspectives (6)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Caring for children with PKU

- Parents and carers of children with PKU also face difficulties with other aspects beyond their child's diet management such as:
  - The need to educate professionals, teachers, other children's parents, their families and other carers as well about the condition and the diet restrictions.
  - Strain on relationships: "*It has strained my relationship of nearly ten years.*"
  - Struggle to get the right support:
    - "*I have no family support or help. And it's extremely scary that if I don't get her food and supplement right, it causes permanent brain damage*";
    - *"CCG don't even know what's available, we've been told a psychologist is available locally which is not true."*
  - Giving up work to dedicate more time to diet management:
    - *"I work part time, but have to work less because he can't eat dinners at school/after school club, so I am worried that he is not eating enough"*
    - *"I gave up work after maternity leave ended as I couldn't trust that someone else who was to care for him would understand the complexity of the dietary controls."*

# Patient and carer perspectives (7)

Comments from: Metabolic Support UK, National Society for Phenylketonuria UK, 2 carers

## Experience with sapropterin

- Adults reported it improved their day-to-day functioning, particularly concentration and mood.

  *"I became happier, could concentrate, had more energy, felt more relaxed, was more organised, could think more clearly. In fact, I felt like superwoman. Whilst I was on Kuvan, I was able to resume my studies as a teacher and qualified."*

  *"An overall positive effect on my health, concentration, sleep and mood".*

- Parents of children reported large increases in their natural protein intake whilst taking Kuvan. Children typically ate no prescription foods and consumed 50% of the usual protein supplements for their age group. Children had a far wider and more socially normally diet as well as greater social freedom participate normal activities as their diet normalised.
- Many parents reported improvements in mood, energy, concentration and behaviour in their children.

  *"After he started Kuvan his teacher noticed the difference. He was alert and less irritable. He paid attention."*

- Health benefits reported in children, increase in bodyweight and growth, improvements in gastro-intestinal symptoms and lessening in mouth ulcers.
- Carers reported a significant easing of burden of care. No need to prepare special prescribed low phenylalanine foods. Some parents able to delegate childcare to others for first time. Carers reported ability to return to work or study, increase working hours, spend more time with other children or other family responsibilities.

# Equality and diversity

- Some people may have greater difficulty adhering to conventional dietary management of PKU and are at higher risk of being unable to control their phenylalanine. Some people may also have difficulty accessing healthcare services. People who face such difficulties include:
  - People with learning disabilities, sensory impairment and cognitive impairment
  - People with co-morbidities such as autism, diabetes, gut disorders
  - People on low incomes, living poor in or insecure housing,
  - Certain ethnic groups including non-English speakers and people from the travelling community
  - People in social care settings
  - Children and young people.
- Women with PKU need to establish controlled phenylalanine levels prior to conception to avoid damage to the fetus.

# Sapropterin evidence base (1)

*Randomised clinical trials (RCTs) not used in economic model*

- Sapropterin has been studied in several RCTs including 3 phase 3 double-blind studies and 1 phase 3b open-label study.
- Study sample sizes were between 45 and 206 participants. All RCTs were of short duration, between 6 and 26 weeks.
- Population inclusion criteria differed across RCTs by:
  - age (<4 years, 4 to 12 years and >8 years)
  - sapropterin response (20–30% reduction in blood Phe levels)
  - blood Phe levels at screening stage (≤480 µmol/L, ≥400 µmol/L and ≥450 µmol/L).
- In 3 trials the intervention was sapropterin plus protein-restricted diet compared with placebo plus protein-restricted diet or protein-restricted diet alone. 1 trial compared sapropterin with placebo where patients were required to adhere to current diet but diet was not part of treatment.
- None of the randomised controlled trials were included in the company model.
- Results from the RCTs show that most patients treated with sapropterin plus protein-restricted diet achieve and maintain target blood Phe concentration levels and increase or maintain their intake of dietary Phe compared to patients treated with protein-restricted diet .

# Sapropterin evidence base (2)

*Registry studies – PKUDOS (in model) and KAMPER (not in model)*

- **PKUDOS:** multicentre observational registry in the United States
- Most recent interim analysis period: 2008–2018
- Sample size: 1,922
- Inclusion criteria:
  - PKU with blood Phe >360 µmol/L
  - People who previously received sapropterin
  - People who were currently receiving sapropterin
  - People who intended to receive sapropterin within 90 days of enrolment
- Patients were assigned to age groups based on age at registry enrolment
- **Used in economic model**

- **KAMPER:** multicentre observational registry in 8 countries in Europe (Austria, France, Germany, Italy, the Netherlands, Slovakia, Spain, Sweden)
- Most recent interim analysis period: 2008–2018
- Sample size: 576
- Inclusion criteria:
  - hyperphenylalaninaemia due to PKU or BH4 deficiency
  - People who were responsive to sapropterin or BH4 and were currently receiving sapropterin at an included site
- **Not used in economic model**

# Sapropterin evidence base (3)

*Registry studies – PKUDOS (in model)*

- Company used data from PKUDOS registry to define two cohorts used in the economic model:
  - **Sapropterin plus protein restricted diet (n=191)**
    - Included patients intending to receive sapropterin within 90 days of enrolment in the PKUDOS registry and with ≥1 pre-sapropterin blood Phe concentration level value available
    - Patients in this subgroup, regardless of sapropterin dose (range 5-20 mg/kg/day), were considered to receive protein-restricted diet in conjunction with sapropterin, as indicated in the sapropterin label [Kuvan SmPC]
  - **Protein-restricted diet alone (n=160)**
    - Included patients who had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin while in the registry

⊙ Is the PKUDOS registry appropriate to provide a comparison of sapropterin plus protein-restricted diet versus protein-restricted diet alone?

# PKUDOS and KAMPER patient characteristics

| | PKUDOS (n=1,922) | KAMPER (n=576) |
|---|---|---|
| **Patients by country, %** | United States (100%) | Spain (23.7%), Italy (20.5%), Germany (19.5%), France (18.2%), Netherlands (9.1%), Austria (3.8%), Sweden (2.4%), Slovakia (2.2%) |
| **Age, years** | | |
| <4, n (%) | [redacted] | [redacted] |
| 4 to <18 years, n (%) | [redacted] | [redacted] |
| ≥18 years, n (%) | [redacted] | [redacted] |
| Unknown | [redacted] | [redacted] |
| **Sex, n (%)** | | |
| Female | [redacted] | [redacted] |

- ERG: people included in the PKUDOS and the KAMPER registry studies are similar to patients with PKU who are likely to be treated with sapropterin in the NHS, except for age (which varies between the two registry studies).
- Clinical expert (technical engagement): Patients included in the PKUDOS registry may be significantly different from cohort of adults with PKU in the NHS due to difficulty of obtaining protein-restricted diet in the US.

⊙ Are the participants in the PKUDOS and KAMPER registries likely to be reflective of patients in the NHS?

# PKUDOS registry results (1)

## *Patients within target Phe levels 120–360 µmol/L*

- Results from the PKUDOS registry show the proportion of patients achieving target Phe levels 120–360 µmol/L were similar over time for all age groups.
- Over time, higher proportions of patients achieved target Phe levels in the younger age subgroups (<4 years and <12 years) than the older age group (≥18 years).
- Number of patients contributing long-term target Phe level data were small.
- **ERG:** Patients were assigned to age groups based on age at registry enrolment.

| Time point | <4 years | <12 years | <18 years | ≥18 years | All patients |
|---|---|---|---|---|---|
| **Patients within guidelines target Phe levels 120–360 µmol/L, n (%)** | | | | | |
| Baseline | | | | | |
| | | | | | |
| 1 year | | | | | |
| | | | | | |
| 2 years | | | | | |
| | | | | | |
| 5 years | | | | | |
| | | | | | |
| 9 years | | | | | |
| | | | | | |

⊙ Are the results of the PKUDOS registry likely to be generalisable to patients in the NHS?

# PKUDOS registry results (2)

## *Patients within target Phe levels 120–600 µmol/L*

- Results from the PKUDOS registry show the proportion of patients achieving target Phe levels 120–600 µmol/L were similar across <4 and ≥18 years age groups, but decreased for <12 and <18 years groups over time. Higher proportions of patients achieved target Phe levels in younger age subgroups (<4, < 12 and <18 years) than older age group (≥18 years).
- Number of patients contributing long-term target Phe level data were small.
- **ERG:** Patients were assigned to age groups based on age at registry enrolment.

| Time point | <4 years | <12 years | <18 years | ≥18 years | All patients |
|---|---|---|---|---|---|
| **Patients within guidelines target Phe levels 120–600 µmol/L, n (%)** | | | | | |
| Baseline | | | | | |
| | | | | | |
| 1 year | | | | | |
| | | | | | |
| 2 years | | | | | |
| | | | | | |
| 5 years | | | | | |
| | | | | | |
| 9 years | | | | | |
| | | | | | |

⊙ Are the results of the PKUDOS registry likely to be generalisable to patients in the NHS?

# KAMPER registry results

- Results from the KAMPER registry show patients were able to achieve Phe target levels of 120–360 and 120–600 µmol/L over time in all age subgroups.
- In the largest subgroup of patients (aged between 4 and <18 years), up to 7 years of follow-up, between [redacted] and [redacted] of patients had blood Phe levels in target range 120–360 µmol/L.
- For patients ≥18 years, median blood Phe concentration levels, up to 7 years, were maintained within the recommended target range of 120 to 600 µmol/L (ranging [redacted] µmol/L).

# Sapropterin dose

- Company stated that mean sapropterin dose for children is 10 mg/kg and for adults is 12.5 mg/kg as per the NHS England Integrated Impact Assessment Report for sapropterin.
- ERG: company proposed values may be underestimates of real-world dosages.
  - Mean sapropterin dose observed in the KAMPER registry was [redacted] (only [redacted] participants were >18 years) and in PKUDOS [redacted] (about [redacted] participants were aged 4–18 years).

| PKUDOS | <4 years [redacted] | <12 years [redacted] | <18 years [redacted] | ≥18 years [redacted] |
|---|---|---|---|---|
| Mean sapropterin dose (mg/kg) | [redacted] | [redacted] | [redacted] | [redacted] |

- Company (technical engagement): dosages in KAMPER reflect clinical practice in the 8 countries that are part of the registry: Austria, France, Germany, Italy, the Netherlands, Slovakia, Spain, and Sweden
- Clinical experts (technical engagement): UK practice is likely very similar to European practice.

⊙ What is the dose of sapropterin used in clinical practice?

# Sapropterin effect on natural Phe tolerance

- Company presented evidence for sapropterin effect on natural Phe tolerance from several studies.
- None of the studies were conducted in the UK or included adult patients and all had small sample sizes (5–25 participants). Information is not provided from one study (Vilaseca 2010) and appears incorrect in another (e.g. patient age in Burlina 2009).

| Reference | Country | N | Age (years) | Mean dose | Natural Phe tolerance (g) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Pre-sapropterin | Post-sapropterin | % increase |
| Belanger 2007 | Spain | 7 | 0–18 | 12.5 | 32.5 | 104 | 220% |
| Burlina 2009 | Italy | 12 | 0–7 | 10 | 52.5 | 175 | 233% |
| Hennerman 2005 | Switzerland | 5 | 0–3 | 10 | 9.5 | 75 | 689% |
| Singh 2010 | Atlanta | 6 | 5–12 | 20 | 42.1 | 147 | 249% |
| Thiele 2012 | Germany | 8 | 5–16 | 20 | 62.9 | 213.1 | 239% |
| Vilaseca 2010 | Spain | 13 | 4–14 | 10 | | 64.15 | |
| Muntau 2002 | Germany | 5 | 4–14 | 8.9 | 18.7 | 61.4 | 228% |
| Muntau 2017 | Germany | 25 | 0–4 | 15 | | 80.6 | |
| Thiele 2015 | Germany | 8 | 6–17 | 14.5 | 49.3 | 220.8 | 348% |
| Tansek 2016 | Slovenia | 9 | 2–10 | 13.05 | 55 | 150 | 173% |
| Scala 2015 | Italy | 17 | 14 | 10 | 58.3 | 279.8 | 380% |

# Sapropterin effect on protein-restricted diet

**ERG:**

- Company assumed that patients taking sapropterin with controlled blood Phe levels can relax their protein-restricted diet through a 71.2% reduction in protein supplements and low protein food.
- ERG were not able to verify that methods used to calculate 71.2% value were robust.
- ERG clinical expert indicates only minor reductions in the amount of prescribed protein substitutes would be expected.

**Technical engagement:**

- 71.2% reduction may be reasonable estimate in patients who are responsive to sapropterin i.e. 30% reduction in Phe levels and doubling of natural Phe intake (ESPKU guidelines).
- [redacted]
- Protein substitutes are unlikely to be removed entirely to allow for some buffer and to ensure patients do not forget the taste or technique associated with protein substitute intake should they need additional protein in times of illness.

- Is a 71.2% reduction in protein-restricted diet reasonable after sapropterin treatment?
- What percentage reduction in protein-restricted diet is expected after sapropterin treatment?

# Evidence for long-term brain damage (1)

*Evidence from company*

- Company captures the impact of irreversible long-term brain damage in the form of IQ reductions (intellectual disability) due to moderate or severe symptoms of PKU.
- Company estimate an average 3-point reduction in IQ per 100 µmol/L increase in blood Phe levels and applied it to different symptoms severities.
  - Data from meta-analysis in early-treated children with PKU aged 0–12 years old (critical period for brain development and maturation) by Waisbren et al. 2007: 1.9 to 4.1-point IQ reduction per 100 µmol/L increase in blood Phe levels.
- Company use estimated IQ reductions to calculate and include utility decrements associated with long-term brain damage in the model.

# Evidence for long-term brain damage (2)

*Clinical expert opinion (technical engagement)*

- Long-term brain damage occurs in children treated in the NHS; however, it is considered a result of reduced adherence to protein-restricted diet.
  - Degree of brain damage in adults with early-treated PKU is not as severe as adults with untreated or late-treated PKU born before treatment or newborn screening programmes were available.
- Very few people with early-treated PKU have significant learning disabilities. More patients have scores which fall more than 1.5 standard deviation below the mean on neuropsychological tests of executive function and processing speed, but the clinical significance of such findings is unclear.
- Brain damage in people with early and continuously treated PKU can manifest as:
  - lower IQ score compared to people without PKU or unaffected relatives
  - clinically relevant neuropsychological impairments (25% of people with PKU)
  - minor neurological symptoms e.g. tremor, brisk lower limb reflexes, mild motor impairment (20–40% of people with PKU).

# Evidence for long-term brain damage (3)

*Clinical expert opinion (technical engagement)*

- Information on long-term brain damage due to PKU is not routinely collected in the NHS.
  - Data on the number of children with PKU referred to early help services and social services is also not collected.
- Additional care needs for people with PKU and long-term brain damage can include:
  - Additional blood phenylalanine monitoring
  - Additional hospital appointments and telephone contacts by health professionals
  - Possible hospital admission
  - School/college: Education, Health and Care plans for learning needs
  - School/college: Additional teacher/teaching assistant time to supervise protein substitute (all children with PKU).
  - Use of home support workers
  - Possible involvement of safeguarding and social services – referral to early help services for patients with very poor phenylalanine control (as per European PKU Guidelines).

# Key issues – clinical effectiveness

- Are there differences in risk between children and adults with this disease?
- Are the dietary requirements the same for children and adults?
- Is the PKUDOS registry appropriate to provide a comparison of sapropterin plus protein-restricted diet versus protein-restricted diet alone?
- Are the participants in the PKUDOS and KAMPER registries likely to be reflective of patients in the NHS?
- Are the results of the PKUDOS registry generalisable to patients in the NHS?
- What is the dose of sapropterin used in clinical practice?
- Does sapropterin allow patients to reduce their protein-restricted diet?
  - What percentage reduction in protein-restricted diet is expected after sapropterin treatment?

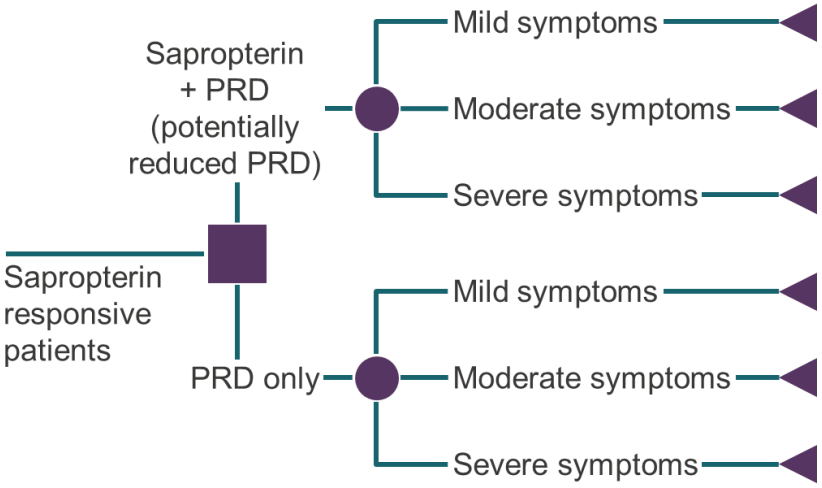
# Key issues – cost effectiveness

- Utilities:
  - Is it appropriate to apply utility decrement for intellectual disability to both children and adults?
  - Are utility decrements for intellectual disability already counted in the utility values assumed for the different PKU symptom states?
  - Are the additional utility gains due to sapropterin treatment included by the company appropriate?
  - Are the health state utility values estimated by the company realistic?
- What is the dose of sapropterin used in clinical practice?
- What is the most likely reduction in protein-restricted diet whilst on sapropterin?

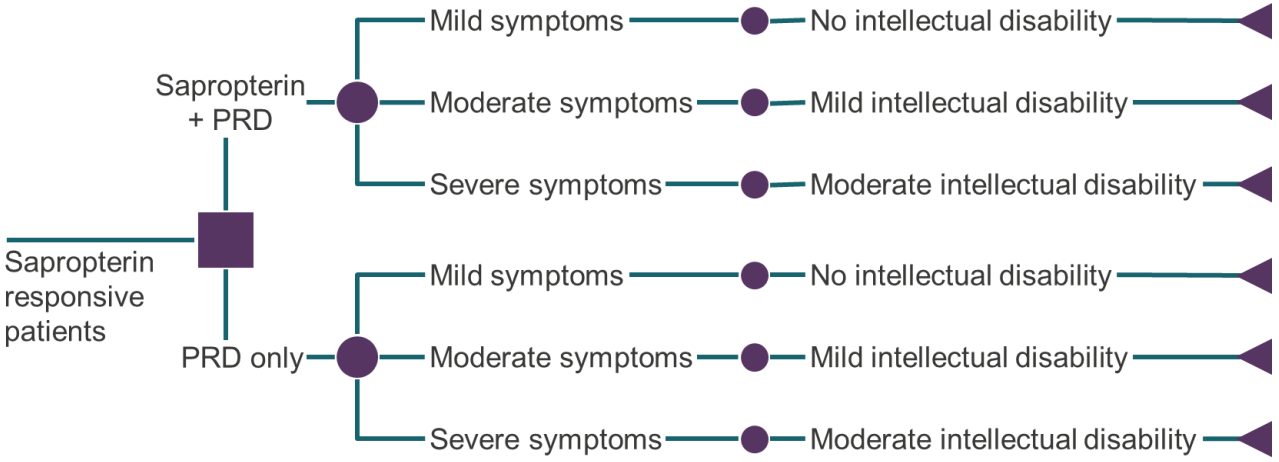
# Model structure

- After technical engagement, company submitted a revised model based on ERG suggestions: decision tree with a 1-year time horizon.
- Cohort split by treatment arm (sapropterin plus protein restricted diet and protein-restricted diet alone).
- 3 health states for each treatment arm based on symptom severity (mild, moderate and severe) and intellectual disability (none, mild and moderate).
- Utilities for each health state calculated using a time-trade off study in a Swedish population.

**ERG suggested model**




**Company revised model (technical engagement)**



# Utilities

- Quality of life was not assessed in sapropterin studies due to difficulty in measuring it in people with PKU. Company obtained health state utility values from time trade-off (TTO) study carried out in Sweden.
  - Hypothetical vignettes (used to represent experience of UK adults and modified for UK children by UK clinicians) were valued by a sample of >1,000 Swedish adults (general population).
- Utility values were validated by UK clinical experts: 3 specialist adult metabolic physicians, 2 specialist paediatric metabolic physicians, and 1 advanced practitioner in metabolic disease and experienced metabolic dietitian.
- ERG:
  - quality of life is difficult to measure in people with PKU because of small patient samples and range of disease states.
  - TTO study not aligned with NICE Reference Case, which is to obtain health state descriptions from patients and ask general public to value health state descriptions.
  - TTO study is best available source of utility values for PKU states ('best available' ≠ 'robust'), but values in TTO study may not represent true utility values of people with PKU.

# Utility decrement for intellectual disability

- Company assumed a utility decrement for intellectual disability based on IQ reduction for patients with moderate or severe symptoms (children and adults).

| Baseline i.e. no PKU symptoms or diet restrictions | 0–17 years | >18 years | Women of child-bearing age |
|---|---|---|---|
| No intellectual disability | [redacted] | [redacted] | [redacted] |
| Mild intellectual disability | [redacted] | [redacted] | [redacted] |
| Moderate intellectual disability | [redacted] | [redacted] | [redacted] |

- **ERG:**
  - Company applied utility decrement to patients of all ages.
  - Only children are at risk of **irreversible** long-term brain damage due to increase blood Phe levels, while adults experience short-term symptoms and **reversible** brain damage.
  - Model has a 1 year time horizon, so:
    - utility decrement may be double-counting decrement already applied for different PKU symptom states.
    - long-term impact of brain damage from uncontrolled blood Phe levels not captured.

# Additional utility gains with sapropterin

- Company included utility gains for all patients with mild, moderate or severe symptoms and for women of child-bearing age receiving sapropterin in addition to:
  - Utility resulting from reductions in PKU symptoms
  - Utility resulting from reductions in protein-restricted diet

| | Mild symptoms | Moderate symptoms | Severe symptoms | Women of child-bearing age |
|---|---|---|---|---|
| **Utility gain** | [redacted] | [redacted] | [redacted] | [redacted] |

- ERG: values are arbitrary and company has not provided justification for including them in their calculation.
  - Increased blood Phe levels can harm the unborn child; however, the extent of lost utility is unclear as is the effect of sapropterin on utility loss.

⊙ Are the additional utility gains due to sapropterin treatment included by the company appropriate?

# Health state utility values

- Company's calculated utility values for people with severe PKU symptoms and on protein-restricted diet are very low and/or negative.

| Group | Symptoms | Protein restricted diet | | | Sapropterin + protein-restricted diet | | |
|---|---|---|---|---|---|---|---|
| | | Intellectual disability | | | Intellectual disability | | |
| | | None | Mild | Moderate | None | Mild | Moderate |
| Children (0–17 years) | Mild | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | Moderate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | Severe | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Adults | Mild | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | Moderate | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | Severe | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

- Comparative examples of low utility levels: adults after major stroke (0.41), treatment-resistant depression (0.30)
- ERG: negative utility values are unusual, but possible; however company has not provided any discussion or justification for using such low values.

⊙ Are the health state utility values estimated by the company realistic?

# Utilities: summary of ERG critique

- The long-term impact of intellectual disability resulting from uncontrolled blood Phe concentration levels is not captured because the model only has a 1-year time horizon.
- Utility gains for people taking sapropterin are arbitrary. Company has not provided justification for including these gains in their model.
- Company assumed that the effect of elevated blood Phe concentration levels on intellectual disability affects both children and adults.
- Applying a utility decrement for intellectual disability may be double-counting; utility values for different PKU symptom states already take into account the effect of cognitive impairment on quality of life.
- Increased blood Phe concentration levels can harm an unborn child; however, the extent of the utility loss is unclear, as is the extent of the effect of sapropterin on utility loss.

# Cost of sapropterin

- Company stated that mean sapropterin dose for children is 10 mg/kg and for adults is 12.5 mg/kg as per the NHS England Integrated Impact Assessment Report for sapropterin.
- ERG: company proposed values may be underestimates of real-world dosages, and consequently, costs of sapropterin.

| Age | Company assumptions | | ERG assumptions | |
|---|---|---|---|---|
| | Dose | Sapropterin cost | Dose | Sapropterin cost |
| 0–3 | 10 mg/kg | [redacted] | [redacted] | [redacted] |
| 0–17 | 10 mg/kg | [redacted] | [redacted] | [redacted] |
| 18+ | 12.5 mg/kg | [redacted] | [redacted] | [redacted] |

⊙ What is the dose of sapropterin used in clinical practice?

# Costs of protein-restricted diet

- Company estimated costs of protein-restricted diet based on expert advice and averaging the cost of three brands.
  - protein substitute: 40 g daily for <4 years, 50g for 4–18 years and 70g for >18 years
  - low protein food: based on weekly dietary requirements for 3 year old weighing 14kg, a 7 year old weighing 22kg and an adult.
- ERG consider the costs of protein-restricted diet are reasonable and have used them in their calculation.
  - However, evidence for company assumption that patients taking sapropterin will reduce PRD by 71.2% is not robust → produced two scenarios 0% and 71.2% PRD reduction.

| Resource use | 0–3 years | | 4–17 years | | ≥18 years | |
|---|---|---|---|---|---|---|
| | Weekly requirement | Annual cost | Weekly requirement | Annual cost | Weekly requirement | Annual cost |
| **Protein substitute** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Low protein food** | | | | | | |
| - Bread | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Flour | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Milk | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Pasta | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Pizza base | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| - Sausage/burger mix | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total** | | [redacted] | | [redacted] | | [redacted] |

# Company base case ICERs

*71.2% reduction in protein-restricted diet, PAS price, 10 mg/kg (children) and 12.5 mg/kg (adults) sapropterin dose*

| Age | Symptom severity | Sapropterin dose | Annual incremental cost | QALY gain | ICER (£/QALY gained) |
|---|---|---|---|---|---|
| 0–3 years | Mild | 10 mg/kg | [redacted] | 0.13 | [redacted] |
| | Moderate | | [redacted] | 0.19 | [redacted] |
| | Severe | | [redacted] | 0.26 | [redacted] |
| 0–17 years | Mild | 10 mg/kg | [redacted] | 0.13 | [redacted] |
| | Moderate | | [redacted] | 0.19 | [redacted] |
| | Severe | | [redacted] | 0.26 | [redacted] |
| ≥18 years | Mild | 12.5 mg/kg | [redacted] | 0.24 | [redacted] |
| | Moderate | | [redacted] | 0.19 | [redacted] |
| | Severe | | [redacted] | 0.27 | [redacted] |
| Woman of child-bearing age | Mild | 12.5 mg/kg | [redacted] | 0.49 | [redacted] |
| | Moderate | | [redacted] | 0.44 | [redacted] |
| | Severe | | [redacted] | 0.52 | [redacted] |

# ERG alternative cost-effectiveness analyses

- ERG: Results generated by the company's cost effectiveness calculation less informative than the ERG's 'alternative cost effectiveness results'. The ERG's model focusses on the main drivers of cost-effectiveness:
  - reduction in protein-restricted diet
  - cost of sapropterin treatment
  - quality of life benefits due to better Phe concentration level control and reduced need for protein-restricted diet
- Several factors are not included in the ERG's calculations, which could mean their alternative cost effectiveness results of sapropterin plus protein-restricted diet are underestimates:
  - carer disutility for parents/carers of children with PKU
  - the prevention of neurological damage to the unborn child
  - the prevention of neurological damage in children from uncontrolled PKU
  - additional healthcare costs from treating symptomatic PKU patients.

# ERG alternative cost-effectiveness results

*No reduction in protein-restricted diet, PAS price, 12.7 mg/kg sapropterin dose*

| Age | Symptom severity | Sapropterin dose | Annual incremental cost | QALY gain | ICER (£/QALY gained) |
|---|---|---|---|---|---|
| 0–3 years | Mild | 12.7 mg/kg | [redacted] | 0.004 | [redacted] |
| | Moderate | | [redacted] | 0.007 | [redacted] |
| | Severe | | [redacted] | 0.018 | [redacted] |
| 0–17 years | Mild | 12.7 mg/kg | [redacted] | 0.004 | [redacted] |
| | Moderate | | [redacted] | 0.007 | [redacted] |
| | Severe | | [redacted] | 0.018 | [redacted] |
| ≥18 years | Mild | 12.7 mg/kg | [redacted] | 0.013 | [redacted] |
| | Moderate | | [redacted] | 0.020 | [redacted] |
| | Severe | | [redacted] | 0.052 | [redacted] |

# ERG alternative cost-effectiveness results

*No reduction in protein-restricted diet, PAS price, 10 mg/kg (children) and 12.5 mg/kg (adults) sapropterin dose*

| Age | Symptom severity | Sapropterin dose | Annual incremental cost | QALY gain | ICER (£/QALY gained) |
|---|---|---|---|---|---|
| 0–3 years | Mild | 10 mg/kg | [redacted] | 0.004 | [redacted] |
| | Moderate | | [redacted] | 0.007 | [redacted] |
| | Severe | | [redacted] | 0.018 | [redacted] |
| 0–17 years | Mild | 10 mg/kg | [redacted] | 0.004 | [redacted] |
| | Moderate | | [redacted] | 0.007 | [redacted] |
| | Severe | | [redacted] | 0.018 | [redacted] |
| ≥18 years | Mild | 12.5 mg/kg | [redacted] | 0.013 | [redacted] |
| | Moderate | | [redacted] | 0.020 | [redacted] |
| | Severe | | [redacted] | 0.052 | [redacted] |

# ERG alternative cost-effectiveness results

*71.2% reduction in protein-restricted diet, PAS price, 12.7 mg/kg sapropterin dose*

| Age | Symptom severity | Sapropterin dose | Annual incremental cost | QALY gain | ICER (£/QALY gained) |
|---|---|---|---|---|---|
| 0–3 years | Mild | 12.7 mg/kg | [redacted] | 0.130 | [redacted] |
| | Moderate | | [redacted] | 0.134 | [redacted] |
| | Severe | | [redacted] | 0.145 | [redacted] |
| 0–17 years | Mild | 12.7 mg/kg | [redacted] | 0.130 | [redacted] |
| | Moderate | | [redacted] | 0.134 | [redacted] |
| | Severe | | [redacted] | 0.145 | [redacted] |
| ≥18 years | Mild | 12.7 mg/kg | [redacted] | 0.141 | [redacted] |
| | Moderate | | [redacted] | 0.148 | [redacted] |
| | Severe | | [redacted] | 0.180 | [redacted] |

# ERG alternative cost-effectiveness results

*71.2% reduction in protein-restricted diet, PAS price, 10 mg/kg (children) and 12.5 mg/kg (adults) sapropterin dose*

| Age | Symptom severity | Sapropterin dose | Annual incremental cost | QALY gain | ICER (£/QALY gained) |
|---|---|---|---|---|---|
| 0–3 years | Mild | 10 mg/kg | [redacted] | 0.130 | [redacted] |
| | Moderate | | [redacted] | 0.134 | [redacted] |
| | Severe | | [redacted] | 0.145 | [redacted] |
| 0–17 years | Mild | 10 mg/kg | [redacted] | 0.130 | [redacted] |
| | Moderate | | [redacted] | 0.134 | [redacted] |
| | Severe | | [redacted] | 0.145 | [redacted] |
| ≥18 years | Mild | 12.5 mg/kg | [redacted] | 0.141 | [redacted] |
| | Moderate | | [redacted] | 0.148 | [redacted] |
| | Severe | | [redacted] | 0.180 | [redacted] |

# Key issues – cost effectiveness

- Utilities:
  - Is it appropriate to apply utility decrement for intellectual disability to both children and adults?
  - Are utility decrements for intellectual disability already counted in the utility values assumed for the different PKU symptom states?
  - Are the additional utility gains due to sapropterin treatment included by the company appropriate?
  - Are the health state utility values estimated by the company realistic?
- What is the dose of sapropterin used in clinical practice?
- What is the most likely reduction in protein-restricted diet whilst on sapropterin?