NICE National Institute for Health and Care Excellence

Chair presentation: Sapropterin for treating phenylketonuria [ID1475]

3rd Appraisal Committee Meeting – Committee A

Lead team: Richard Ballerand, Stephen Sharp

Chair: Jane Adam

ERG: Liverpool Reviews & Implementation Group

Technical team: George Braileanu, Joanna Richardson, Janet Robertson

Company: BioMarin

8th June 2021 – virtual meeting

Committee's considerations

Committee considerations on cost-effectiveness results

- Sapropterin is likely to be cost effective in children under 18 only when using a dose of up to 10 mg/kg.
- Sapropterin has not been shown to be cost effective in adults with PKU.
- The committee was unable to consider women who are pregnant or planning to conceive separately, and welcomed further comment and evidence on this group.
- Recommending sapropterin for certain groups of adults cannot be justified given the cost-effectiveness estimates.

ACD preliminary recommendation

Sapropterin is recommended as an option for treating hyperphenylalaninaemia that responds to sapropterin in people with phenylketonuria (PKU), only if:

- they are under 18
- a dose of up to 10 mg/kg is used
- the company provides it according to the commercial arrangement.

NICE methods guide (1)

- 6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:
  - **The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.**
  - **Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.**
  - **The innovative nature of the technology**.
- 6.3.4 As the ICER increases in the range of £20,000 to £30,000 per QALY gained, the Committee's judgement about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed in section 6.3.3.
- 6.3.5 Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed in section 6.3.3.

NICE methods guide (2)

- 6.2.15 The Appraisal Committee takes account of how the incremental cost effectiveness of the technology being appraised relates to other interventions.. potentially applied in the NHS. ….their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals.

- 6.2.18 They will consider carefully which individuals benefit most from the technology and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness. The Appraisal Committee may recommend the use of an intervention for subgroups of the population only when there is clear evidence that the characteristics defining the subgroup influence the effectiveness and/or cost effectiveness of the intervention.

Company base case ICERs *(ERG corrected algorithm errors [adults and women of child-bearing age])*

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]	0.20	[redacted]
	Severe		[redacted]	0.30	[redacted]
Woman of child-bearing age	Mild	12.5 mg/kg	[redacted]	0.49	[redacted]
	Moderate		[redacted]	0.45	[redacted]
	Severe		[redacted]	0.55	[redacted]

ERG alternative cost-effectiveness results (Committee's preferred scenario)

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]

Why (according to the company and ERG) is it cost effective by NICE criteria in children but not adults?

- **Health benefits**: Modelling shows more or less equal health benefit for children and adults, i.e. **both** benefit from a reduction in symptoms from high phe *and* from not having to stick so rigidly to the diet. However the committee is aware that the developing brain is particularly susceptible to permanent damage that is not modelled.
- **Costs**: Company prices the drug in mg per kg body weight, so the costs escalate at you grow from child to adult, and the dose also increases from 10mg to 12.5mg
- **Results (list price): discount is confidential**
- **Children: £21,799 per year** (weight 30 kg, sapropterin dose: 10 mg/kg/day)
- **Adults: £65,396** (weight 75 kg, sapropterin dose: 12.5 mg/kg/day)
- Incremental cost effectiveness ratio (ICER) = cost per unit of health gain (QALY)
- To have an ICER for adults equal to that for children it would have to be several times more beneficial for adults than children, but the committee considered that it had more potential benefits in children than adults
- **Is it really not cost effective for adults: have heath benefits not been fully counted so the ICER could be within accepted limits for cost effectiveness? (NICE cannot alter the costs, this is a company decision)**

ACD consultation responses

- Consultee comments from:
  - Company (BioMarin)
  - National Society for Phenylketonuria UK (NSPKU)
  - British Inherited Metabolic Diseases Group (BIMDG)
  - Royal College of Physicians (RCP)
  - Patient experts nominated by NSPKU
  - Clinical experts nominated by NSPKU, British Dietetic Association, BIMDG and RCP

- NSPKU – patient forum (126 responses for children and teens, 117 responses for adults)
- Web comments (94 responses)
- Public (not web) comments (55 responses)

Results from thematic review (1)

- A thematic review of the 401 comments received was conducted and included in the papers. The headline themes are outlined here.
- Stopping treatment with sapropterin at 18 years of age (92% of all responses)
  - 95% of respondents disagreed, questioned or expressed concerns about the decision to stop treatment with sapropterin at 18.
- Occurrence of brain damage in adults (70% of all responses)
  - 90% of respondents highlighted that NICE's statements about brain damage in adults are contradictory and that they do not agree with NICE's conclusions.
- Maternal PKU (59% of all responses)
  - 61% of respondents disagreed with or expressed concerns about the decision to not recommend treatment with sapropterin for women with PKU.
- Discriminatory draft guidance (55% of all responses)
  - 84% of respondents felt that NICE had not considered treating people fairly and highlighted that the draft guidance was discriminatory.

Results from thematic review (2)

- Headline themes continued…
- Impact of PKU and PKU diet on carers and family (61% of all responses)
  - 66% of respondents indicated that managing PKU and the PKU diet affects the entire family.
- Living experience of adults with PKU (53% of all responses)
  - 88% of respondents indicated that PKU and the PKU diet have a substantial effect on all aspects of adults' lives.
- Dose limit at 10 mg/kg (24% of all responses)
  - 44% of respondents questioned the dose limit or indicated that it should not be imposed.
- Sapropterin patent expiry and future generics (2% of all responses)
  - 100% of respondents indicated that the patent exclusivity for sapropterin has expired and that generics are currently being produced, which are likely to be cheaper and therefore more cost-effective than Kuvan.

Results from thematic review (3)

- Further themes submitted include:
- Missing costs from cost-effectiveness model (43% of all responses)
- Experience of PKU diet (42% of all responses)
- Comorbidities (13% of all responses)

Key discussion points

- Is it unreasonable for treatment to stop at 18 years of age?
- Is it unreasonable to recommend a dose of up to 10mg/kg for children?
- Has the due regard been given to the need to eliminate discrimination?
- What are the risks of uncontrolled Phe in adults?
- Are there additional factors (such as comorbidities and caregiver quality of life) that need to be accounted for in the cost effectiveness analysis for some adults?
- How to take account of risks in pregnancy and harm to the unborn child?

Stopping treatment at 18: summary

- Switching from sapropterin to protein-restricted diet is likely to put additional pressure on adolescents while they are trying to adjust to the transition from paediatric to adult PKU health services
  - Adult PKU health services are not equipped with special kitchens where adults can learn how to prepare, cook and maintain a protein-restricted diet
- It is unclear how treatment with sapropterin will be stopped, for example, if it will be phased out or abruptly interrupted
- Learning to manage a protein-restricted diet presents an additional challenge for adolescents who are also in the process of moving out of their parents' home, going to university, starting a job or family
- Switching from sapropterin to protein-restricted diet at 18 would be very difficult to almost impossible because of the extremely restrictive nature of the diet and a lack diet adjustment and preparation habits (which are normally formed during childhood and adolescence)
- The time needed to adjust to the protein-restricted diet and gain control of blood Phe levels may potentially impact brain development and maturation after 18

Stopping treatment with sapropterin at 18

Transition to adult PKU health services (1)

- “I was given support all through my education but ..at 18 that is where the support stops. You are now considered an adult and that you should be finding ways of helping yourself. With all mental illness and learning difficulties.. the services to help are just simply not there in the same way that they are there for children.” – public comment
- “Transition services for children with PKU are not robust with some [geographical] areas lacking fully developed adult services. It is very common for young people to experience a failure to manage their PKU at this life stage with impacts on their mental health and education… The withdrawal of sapropterin would involve a young person having therapy withdrawn at a developmentally inappropriate time – and needing significant input to attempt to learn to manage PKU via strict diet therapy for the first time. Those resources do not exist.” – patient expert comment
- “By stopping sapropterin, patients will require intensive dietary education at the age of 18 years. They will need considerable re-education with a new clinical team of adult specialists that has not had time to establish trust and rapport with their patients. This will have financial implications that have not been calculated in the model.” – clinical expert comment

Stopping treatment with sapropterin at 18

Transition to adult PKU health services (2)

- “Children’s clinics are often equipped with kitchens to teach the children to cook PKU recipes and demonstrate new products. Most adult PKU clinics are an add-on to another department and don’t have the necessary facilities for dietary therapy training. Neither child or adult services normally have dedicated mental health teams and due to the extra load on the mental burden of transition, therefore it would be essential to see a requirement of psychological care being added.” – patient expert comment

Stopping treatment with sapropterin at 18

Unclear how treatment will be stopped

- “Abrupt withdrawal of sapropterin, with the concomitant need for more severe dietary restriction in order to maintain target phenylalanine levels, at this time would be needlessly distressing and disruptive, and might well end up having a real effect on the subsequent course of young people’s lives. I think more sensitive consideration needs to be given to when and how treatment would be withdrawn.” – clinical expert comment
- “The draft guidance does not consider or provide any guidance to the NHS as to how treatment would be stopped in practice, how the NHS would implement the reintroduction of the ultra harsh low protein diet to a patient who has not grown up with the diet and has no “taste” for it. It is not stated whether the transition would take place in child or adult care services and no costings for additional services have been factored into NICE’s cost analysis.” – public comment
- “A big question I ask, is whether Kuvan would be reduced gradually as people approach 18 years of age or whether it would be cut off completely on the 18th birthday. Is there any evidence or research into how Kuvan should be reduced or stopped?” – public comment

Stopping treatment with sapropterin at 18

Moving out, going to university or starting job/family (1)

- “It needs to be realised that 16 to 25 are hugely important years… You decide your career, the next step of your education, from school to college to university, making new friends and worrying about your sexual health, finding a job, leaving parents, moving in with your partner or friends and figuring out who want to be as a person…... I think there is a very high chance that any person growing up with PKU will go off diet around these ages, as during these times, leaving your parents or going to university tends to be people's experimental years… I always joke that as teenagers some people do sex, drugs and rock’n’roll but I didn’t do that, I did doughnuts and pizza.” – public comment
- “Life does not get easier because you’ve suddenly turned 18, you are now potentially by yourself, organising a diet that your parents had managed for you your whole life, that your parents had 18 years' worth of experience on how to cook, to talk to people about it, to manage the symptoms and off days. You now have to balance full time education, a full-time job, relationships, friendships, managing a household, managing your own exercise and mental health and having to make every meal, count every gram of protein, resist temptation of fast eating, fast food and the social pressure that comes with eating a meal.” – public comment

Stopping treatment with sapropterin at 18

Moving out, going to university or starting job/family (2)

- “At 18 many are leaving home to go to university and starting work. That is not the time to have a major change in diet which may lead to poorer concentration, low mood, anxiety etc… We also believe that a PKU sufferer not brought up with the various supplements needed in greater quantities after 18 would find them very hard to stomach as they are extremely unpalatable. This change after 18 would result in many going off diet and having much poorer health. We well remember the difficulties faced when our daughter went away to university and despite having prepared well by learning to cook and manage the diet, she experienced a great deal of anxiety and stress on trying to cope with the diet, follow her studies and adapt to university life.” – public comment
- “Adults with PKU who have showed much academic potential as teenagers describe dropping out of university because they have been unable to adhere to their only treatment option of dietary management with consequential result of loss of metabolic control which then impacts on executive function and mental health.” – clinical expert comment

Stopping treatment with sapropterin at 18

Switching to protein-restricted diet (1)

- "NICE appears to have a simplistic view or indeed has not regarded how eating behaviours are shaped. A child that has learnt what foods they can eat whilst being treated with Kuvan will not simply be able to unlearn those food choices. Habitual behaviour related to food choices is guided by information about immediate consequences (such as taste, likeability and familiarity) and it is not sensitive to representations of delayed outcomes (such as the knowledge that eating 2 biscuits would not fall within the day's protein restriction). Habits (e.g., the routine of living with PKU with sapropterin treatment) are performed automatically and non-consciously. Going against the grain of habit (life without sapropterin and having to learn new dietary habits) is difficult, requiring sustained effort (executive cognitive control, bearing in mind high Phe levels reduces cognitive control) to monitor and abandon existing habits, and to acquire new ones." – patient expert comment
- "A person's ability to select food and to make decisions about how much to eat is affected by memory for specific eating episodes (episodic memory). Thus, NICE cannot expect a person that has previously been treated with sapropterin to select low protein foods with ease and without giving thought to the cognitive processes that underpin food selection." – patient expert comment

Stopping treatment with sapropterin at 18

Switching to protein-restricted diet (2)

- “18-year-olds accustomed to a very relaxed diet through using Kuvan [sapropterin] will not have the coping skills to switch to a strict diet which involves constant preparation of meals, precise measurement of all foods, constant management of prescriptions, regular self-administered blood tests, and difficulties in participating in social occasions based around food, including eating out in restaurants. It will lead to people not continuing the diet, being lost to treatment and having health issues related to high phenylalanine levels in adulthood. NICE has ignored this issue completely.” – public comment
- “It is irrational to relax protein intake in childhood, only to restrict it later in adulthood. It is expected that the proposed recommendation of NICE will lower patient motivation at the age of 18 years; it could also lead to patients failing to attend their metabolic clinics as they consider they are not being offered a realistic or workable treatment option.” – clinical expert comment
- “The committee did not perform any enquiry into whether into the risks of withdrawing sapropterin for young people aged 18. There is no evidence that suggests that individuals can reliably return to the PKU diet once they have stopped. In fact, there is evidence that returning to the PKU diet is rarely successful.” – patient expert comment

Stopping treatment with sapropterin at 18

Impact on brain development and maturation after 18

- “Eighteen years is a difficult developmental age when physical growth stops but brain function continues to develop. The brain is still maturing, and strengths and vulnerabilities continue to emerge. It is a time of life when little is normative. It is a period of frequent change that covers many aspects of life: including hospital transition, leaving school, living independently, going to work or university. It is a time when individuals face significant challenges and are expected to assume new responsibilities and obligations.” – clinical expert comment
- “Early adulthood is generally a time of heightened psychological vulnerability and onset of serious mental health disorders, with higher rates of psychological distress; problems compounded by failure to recognize illness or to seek treatment. Suddenly exposing patients with PKU to higher phenylalanine levels at the age of 18 years, may increase the risk of mental health issues. It may lead to mood instability, impulsivity, recklessness, and anger.” – clinical expert comment

Brain development beyond 18 years

- “Neuroimaging research demonstrates that brain development continues beyond the age of 18. For example, the frontal lobes, home to key components of the neural circuitry underlying “executive functions”, are the last areas of the brain to mature and may not be fully developed until halfway through the third decade of life (Sowell et al 1992). Indeed, the draft accepts that, “adolescents and young adults may still be at risk of long-term brain damage from high Phe levels, because brain development does not stop until around age 25.” – patient expert comment
- “There is plenty of academic research out there which shows that the brain continues to develop beyond the age of 18 years of age. It is widely believed that not only does the brain develop well into our mid-twenties but may continue up to age 30 years.” – public comment
- “NICE says there is no risk of permanent damage to the brain after the age of 18, but this is contradicted by other statements made by NICE in the document which recognise that permanent harm can occur after the age of 18 and that brain development continues until age 25.” – public comment

Discussion point 1 – Is it unreasonable for treatment to stop at 18 years of age? (1)

- This age is one of transition for many young people, which is very challenging in many cases.
- Adult services take over from children's services.
- Sapropterin dose is higher as an adult and patients weigh more therefore the cost of sapropterin as an adult is greater. At the current price of sapropterin, the company's ICERs are not considered to an effective use of NHS resources in people over the age of 18.

ERG cost effectiveness results (assuming 71.2% reduction in protein-restricted diet and PAS price)

Age	Symptom severity	Sapropterin dose	Annual incremental cost	QALY gain	ICER (£/QALY gained)
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]

- The company did not conduct any analysis up to 25 years of age.

Discussion point 1 – Is it unreasonable for treatment to stop at 18 years of age? (2)

- After the ACM2 the ERG modelled a scenario for under 25 year olds, which combines the 18-24 year olds with the children in the model. The results are based upon the average sapropterin costs, reduction in PRD costs and reduction in symptoms with sapropterin for an average individual aged 0-24.
- The results use an average dosage of 10mg/kg, noting that the average dosage for people over 18 years is higher than 10mg/kg and the benefits for people aged 18-24 years in the model are based upon this higher dosage. The ERG highlight that the assumption has to be made therefore that there are no additional benefits from dosages higher than 10mg/kg for people aged 18-24 years.

Age	Symptom severity	Sapropterin dose	Annual incremental cost	QALY gain	ICER (£/QALY gained)
0–17 years	Mild	10 mg/kg	[redacted]	0.130	[redacted]
	Moderate		[redacted]	0.134	[redacted]
	Severe		[redacted]	0.145	[redacted]
<25 years	Mild	10mg/kg	[redacted]	0.133	[redacted]
	Moderate		[redacted]	0.138	[redacted]
	Severe		[redacted]	0.155	[redacted]

– What are the risks of irreversible brain damage in young people aged between 18-25 years?

Dose limit at 10 mg/kg

- Dose limit at 10 mg/kg will prevent children with PKU from getting sapropterin if they are only responsive to higher doses up to 20 mg/kg.
- Dose limit at 10 mg/kg may indirectly discriminate against children with disability.

Dose limit at 10 mg/kg

Dose limit preventing access to sapropterin (1)

- “The introduction of a limit of 10 mg/kg will exclude some children who are Sapropterin responsive from treatment – evidence suggests that more patients will respond to doses of 20 mg/kg than 10 mg/kg [Muntau et al 2019], although the proportion of patients who only respond to 20 mg/kg will depend on individual genotype and method of response testing. Thus, the numerical impact of this on under 18-year-olds in the UK is unclear.” – clinical expert comment
- “I would question the decision to limit the dose to 10 mg/kg. Weight appears to have been given to the opinion of one clinician as stated on page 15 stating that little difference in outcome was noted with increase in dose from 10 mg/kg to 20 mg/kg. Muntau et al (2017) showed that in a phase IIIb trial only 2 of 27 had dosage increased to 20 mg/kg. This was deemed necessary to achieve Phe tolerance >20% above baseline. I would suggest that by limiting the dosage 7% of children who would have a clinically significant response would be denied sapropterin treatment with all the benefits conferred.” – public comment

Dose limit at 10 mg/kg

Dose limit preventing access to sapropterin (2)

- “NSPKU agrees that clinicians in the UK will prescribe more efficiently than in the US and that an average dose of 10 mg/kg is appropriate for the cost analysis. However, NSPKU believes that clinicians should be able to prescribe within the marketing authorisation, which ranges from 5 mg/kg to 20 mg/kg.” – public comment
- “The policy proposes to limit the dose to 10 mg/kg because the evidence is that this is the average treatment. This dosage limit would be severely harmful to some patients and is unnecessary. There are many patients who require a higher dose for clinical effectiveness so for those patients the dose limit would render treatment ineffective. The limit is unnecessary because the average dose is 10 mg/kg, so this will average out over the cohort.” – public comment
- “While my daughter was on the sapropterin trial she was started on a 10 mg dose which did not reduce her blood Phe levels. She was increased to 20 mg of sapropterin, and this was the dose that she responded to. After speaking with her metabolic specialist, we were informed that she has the 30% reduction (requirement for sapropterin response). Therefore, if my daughter was to get sapropterin now, even though we know sapropterin works for her it would have little or no effect on her as the dose is too low. This could be the case for many children they will respond to sapropterin but will not be able to benefit as the correct dosage is not being made available by NICE/NHS England.” – public comment

Dose limit at 10 mg/kg

Dose limit discrimination

- “The dose limit is indirectly discriminatory as disabled children are likely to have a higher body mass due to their inability to exercise etc. NICE should allow the clinician to determine the dosage on the basis of what is in the best interests of the patient.” – public comment

Discussion point 2 – Is it unreasonable to recommend a dose of up to 10mg/kg for children?

- Committee heard from the clinical experts at ACM1:
  - In their experience using between 10 mg/kg and 20 mg/kg resulted in little difference in outcome. Increasing sapropterin dose does not improve efficacy because response to sapropterin primarily depends on the level of PAH activity and mutations, not the dose.
  - Patients whose PKU responds to sapropterin increase their tolerance to natural Phe consumption by 2 to 4 times, regardless of dose.

ERG cost effectiveness results (assuming 71.2% reduction in protein-restricted diet and PAS price)

Age	Symptom severity	Sapropterin dose	Annual incremental cost	QALY gain	ICER (£/QALY gained)
0-17 years	Mild	10mg/kg*	[redacted]	0.130	[redacted]
	Moderate		[redacted]	0.134	[redacted]
	Severe		[redacted]	0.145	[redacted]
0-17 years	Mild	12.7mg/kg	[redacted]	0.130	[redacted]
	Moderate		[redacted]	0.134	[redacted]
	Severe		[redacted]	0.145	[redacted]

* The scenario the committee based its decision making on in the ACD

Should committee consider recommending a higher dose for children? Up to 20mg/kg? 10mg/kg is the average dose given. Do some children get less than 10mg/kg?

Discriminatory draft guidance

- Treatment for PKU is lifelong and continues beyond 18 years so it is discriminatory against adults to recommend sapropterin only for children
- Draft guidance is discriminatory against adults with PKU who are unable to manage their diet due to disability
- Draft guidance is discriminatory against adult women who shoulder the burden of care

Discriminatory draft guidance

Discrimination against adults (1)

- “The European Guidelines for the Treatment of PKU (EGTPKU) stipulates that PKU patients of all ages require of treatment for life. It is therefore discriminatory against age and goes against the recommendations of the EGTPKU to restrict access to Kuvan to PKU patients under 18 years and refuse access to the only other treatment for PKU available in the UK, to PKU patients over the age of 18.” – public comment
- “The discrimination of the drug only being offered to children is wrong. PKU doesn’t stop at 18! The drug would make a huge difference to the lives of adults. There is a lot of information and evidence of adults struggling in later life with anxiety, depression, phobias, poor memory. This is extremely worrying for my own child when they move into adulthood and need to cope at university or in the workplace. The drug would support them but if taken away at 18, the effects would be detrimental.” – public comment
- “I have concerns about the need to stop sapropterin treatment at the age of 18. I can understand the argument that it is most important to obtain strict metabolic control in childhood, as the risk of irreversible damage to the brain and permanent loss of IQ is reduced after the age of 10 and is not present in adults. I also agree that treating adults would not be cost effective as the potential benefits from treatment are much less and the patients weigh much more. However, neither of these considerations would lead to a decision to stop treatment at the age of 18.” – clinical expert comment

Discriminatory draft guidance

Discrimination against adults (2)

- “I think NICE have only considered one element of life, which is brain development in children, but life does not end when the brain stops developing. Adult life is far more complicated, harder, lonely, you have far more responsibility, a job where your mistakes could cost the company money or potentially lives. You no longer have the unwavering support of your parents who control every part of your life for you. You’ve got to figure out who you are, what you want to be, how you want to contribute to society, as well as then cooking every meal from scratch, taking substitutes drinks, tablets every day, taking monthly blood tests, organising weekly prescriptions for food, doing 6 monthly doctor appointments, how is this any less important than a developing brain?” – public comment
- “It appears that NICE’s recommendation to terminate treatment at aged 18 is because the ERG cost model did not incorporate the benefit of preventing long-term brain damage after the age of 18. Why this was not factored in does not make sense especially when one reads the discussion of clinical considerations accepts that long term brain damage has the potential to occur after the age of 18. Therefore, NICE’s decision is discriminatory as the difference in treatment between age groups has not been properly considered or justified.” – patient expert comment

Discriminatory draft guidance

Discrimination against disability and gender

- “It is discriminatory against disability not to offer an alternative treatment to diet to adults with PKU because they are struggle with or unable to manage the dietary treatment because of their disability.” – public comment
- “Adults with PKU who are untreated or undertreated effectively have a disability and, under this guidance, would not be offered fair and equal access to service. The draft guidance seems to be neither compliant with s13G of the National Health Service Act 2006 nor the Public Sector Equality Duty section 149 of the Equality Act 2010.” – public comment
- “It is discriminatory against gender to not consider the quality of life of the carers of people with PKU, which is a life-long commitment and a heavy burden of care which, as has been shown in studies, mainly falls on the mother, and it is the mother who often has to give up her career and income to care for their PKU child.”

Discussion point 3 – Equality Issues (1)

Public Sector Equality Duty

- The Public Sector Equality Duty requires public bodies and others carrying out public functions to have due regard to the need to eliminate discrimination, to advance equality of opportunities and foster good relations.
- The duty applies to all nine areas of discrimination listed in the Equality Act 2010
  - Age
  - Disability
  - Gender reassignment
  - Pregnancy and maternity
  - Race
  - Religion or belief
  - Sex
  - Sexual orientation
  - Marriage and civil partnership

Discussion point 3 – Equality Issues (2)

- The draft guidance is discriminatory on the grounds of age. However, this is lawful if in pursuit of a legitimate objective.
- The committee's draft guidance recommending for children was based on the differences in the benefits of sapropterin in children versus adults and the differences in the costs of sapropterin in children versus adults.
- The committee was presented with ICERs for people young than 18 and older than 18 years. On this basis the committee was minded to recommend to those under 18 years as they considered this to be a cost-effective use of NHS resources (which is considered a legitimate objective).

Discussion point 3 – Equality Issues (3)

- The committee was aware that there were protected groups within the adult population who have particular difficulties with maintaining Phe levels with diet alone.
- Overall sapropterin is not cost effective in the adult population.
- No specific groups have been identified in consultation that would override this consideration or in whom sapropterin could be used cost-effectively.

Brain damage occurring in adulthood

- Brain damage or changes experienced by adults with PKU (during adulthood) are not completely reversible upon restarting protein-restricted diet.
  - Lowering Phe levels results in brain damage being improved (sometimes only partially), but not reversed.
- Brain development continues beyond the age of 18, possibly until 25 or even 30.
- Previous clinical practice recommended that protein-restricted diet could be stopped as early as age 8 on the assumption that there was no risk of brain damage, which has been proven incorrect and has led to worse outcomes for people with PKU.

Brain damage occurring in adulthood

Brain damage in adults not fully reversible (1)

- "There are a small but increasing number of case reports in recent years that provide evidence that some adult PKU patients develop severe neurological symptoms in later adulthood. Some of these cases are from the UK. They demonstrate that severe decline in neurological function occurs despite relatively normal function for a substantial period. They demonstrate the vulnerability of the brain to high phenylalanine levels. It is possible that there are many similar cases, but they remain unreported by clinics. Not all symptoms have reversed on dietary treatment. Also, authors generally do not report the longer-term outcome of these cases." – clinical expert comment
- "A recent paper provides a review of neurological cases which presented in adulthood. This reviewed 8 new cases of neurological manifestations in adults with PKU with 22 cases reported in literature. These were adults – mostly early diagnosed and treated who presented with debilitating neurological symptoms such as the inability to walk and visual loss. MRI scans showed white matter lesions in the brain. The review showed that reinstituting treatment to lower phenylalanine levels could improve symptoms. However, the review does not support the statement that the adults' problems were all reversible. The cases studies generally show partial improvements, some adults still had brain lesions, sight loss, tremor and other neurological symptoms. The damage was improved with treatment but not reversed." – patient expert comment

Brain damage occurring in adulthood

Brain damage in adults not fully reversible (2)

- “The literature suggests that white matter changes caused by high Phe in the brains of adults with PKU is more reversible than brain damage incurred in children. However, there is no conclusive evidence that brain damage in adults is fully reversible. For example, Cleary published on this 26 years ago, and 2 months ago, further imaging evidence (provided by Clocksin et al 2021 in MGM [Molecular Genetics and Metabolism journal]) have found improvements following Phe level reduction in adults. However, even after improvement, white matter integrity in the PKU patients in these studies continued to be compromised relative to healthy non-PKU individuals.” – patient organisation comment
- “They [NICE] make the statement, there isn't ‘irreversible brain damage in adults with PKU’. How much data and published papers do they have to make that conclusion? I would be extremely weary of making such a statement. It would be like saying, if you gave a child lots of alcohol, and then the same to an adult, only irreversible damage would take place in a child not and adult, which I believe is not true.” – public comment
- “Whilst some of the effects of brain damage on PKU adults may be reversible by resuming dietary therapy, many effects, such as depression and anxiety, may take years and much therapy to overcome. They may never get over it. The stress that many young adults feel from such a restricted diet in childhood literally traumatizes them and that is not something that instantly disappears.” – public comment

Brain damage occurring in adulthood

Past practice leading to worse outcomes

- “Going back only 30–40 years ago, the NHS deemed that it was safe for children as young as 8 years old to come off diet without risk to their brain. We now know this was wrong. Back then, we did not have the foresight that we have now. We now know that we do not know everything there is to know about the human brain. It is therefore inconceivable for NICE to conclude that there is no risk of irreversible brain damage to adults with PKU.” – public comment

Discussion point 4 – What are the risks of uncontrolled Phe in adults? (1)

- The committee noted and heard at ACM1 that there was potential for long-term irreversible brain damage in children (especially up to the age of 12) if a child's Phe levels were not kept within limits.
- For adults, the committee heard that damage could occur when a person's Phe levels were not kept within limits but that this damage was reversible when diet was resumed and Phe levels returned to within the advised range. The committee also heard that some adults choose to stop the diet.
  - Is the diet as restrictive for adults as children?
  - Do 40% of adults stop taking the diet?
  - Can irreversible brain damage occur in adults if Phe levels are not maintained? If so, how great is that risk?
- Agreement: there is a significant risk of permanent brain damage related to uncontrolled PKU levels in childhood when the brain is developing, so early diagnosis and dietary control is critical.
- Accepted: in adulthood some people have cognitive symptoms related to raised PKU levels
- Unresolved: In the NHS with early identification and treatment, what is the risk of irreversible permanent brain damage beginning in adult life compared with the risk in childhood?

Discussion point 4 - What are the risks of uncontrolled Phe in adults? (2)

- Benefits included in the model are:
  1. Related to improvements related to better control of Phe levels
  2. Related to benefits of a less strict diet
  3. But are any new permanent and irreversible changes included in either the company or ERG's model ?
- Both the company and ERG's model show more or less equal benefits for children and adults, but the drug costs for adults are much higher because they weigh more, so it is not cost effective in adults.
- Would sapropterin given to all adults, prevent irreversible damage occurring during adulthood (which would have happened without sapropterin), have an additional, currently uncounted QALY gain sufficient to reduce the ICER to an acceptable level?
- Is there a group of adults for whom it would be cost effective?

Living experience of adults with PKU: summary

- Adults with PKU have high caregiving needs and often rely on their families and friends for support with managing the PKU diet.
- Individuals with untreated and late-treated PKU may face numerous barriers in maintaining a strict PKU diet and control of Phe blood levels due to PKU related learning disabilities or to their care arrangements.
- Adults with PKU have comorbidities (including learning disabilities and PKU-related anxiety or depression) which can prevent them from engaging with care services and maintaining strict diet.
  - There are also other comorbidities such as weight-related problems, respiratory and gastric conditions and other metabolic conditions which may be in part prevented by exercise (possible through relaxation of diet).

Living experience of adults with PKU

Caregiving needs: young adult (1)

- “He [my grandson] struggled to cope with his PKU [as an adult]. He was leaving home for the first time to attend university several hours away and struggling to get on top of his mental health, managing his prescription foods, organising deliveries from the chemist, coordinating his own medical appointments, cooking the foods, storing all the foods and medication he needed, learning to study independently, manage his lectures and timetabling, housework etc. - all by himself for the first time, which was extremely daunting for him! Although, my daughter supported, encouraged and prompted my grandson to the best of her ability with managing his PKU, he found it very difficult and failed his first-year exams. He then had to take time out from university and come back home where my daughter helped him get back on top of his health. He was given a special dispensation and was allowed to continue to do his second-year studies; however, despite all the family's best efforts, the PKU got the better of him and once again, he had to drop out of university. Throughout this period, he has been seen by adult mental health care services and received therapy for depression, social withdrawal and anxiety. For my grandson, it was clear that the only way he would be able to finish his degree would be to transfer to a local university where he could live at home whilst he studied, be supported by his family to manage his condition and attend therapy for his mental health.” – public comment

Living experience of adults with PKU

Caregiving needs; reliance on parents (2)

- “I have struggled considerably with my diet whilst leaving the comforts of home. I no longer had my mother preparing meals, ordering prescriptions, picking up prescriptions and helping me manage my PKU. After managing to secure a place at university I was petrified of the idea of attempting to live on my own with my diet. I did not succeed on many occasions. It is simply impossible to get it right all the time as an adult. You come home late, forget to eat at the right time, forget supplements or you have simply miscalculated how many supplements you need. Then the PKU begins to affect your success, your relationships with friends. Relationships that you rely on are affected, if not lost, professors notice a decline in concentration, a glazed look in your eyes.” – public comment
- “Then there is the fact that one has to continuously make this stuff [PKU diet food]. I am greatly fortunate I have parents who enjoys cooking immensely and derive happiness out me enjoying the tasty food they cook, but I can’t imagine others are as lucky as me to have essentially “staff members” on standby dedicated to cooking low-protein food.” – public comment

Living experience of adults with PKU

Caregiving needs: family support (3)

- "A man, born in the late 1960s and diagnosed via the "nappy test". He ceased dietary treatment in late teens and now has executive functioning problems and short-term memory problems that impact everyday activities. He returned to diet with the support of his clinic to improve his symptoms. His partner and mother supports him to maintain dietary treatment, for example by organising his meals and shopping and reminding him to have his supplements. He could not manage this without support as he struggles with organisation." – patient expert comment
- "I am aware of patients with PKU who are supported by informal family care. During the pandemic, our [NSPKU] helpline became aware of patients who significantly declined because this family care was no longer available – indicating that informal family care masks how many patients are reliant on care that would otherwise have to be publicly funded." – patient expert comment
- "I know many people living with PKU who share the same story as I do, of going off diet because they felt so overwhelmed with the pressures off it, because they were away from their family who looked after their diet for all them all their years or because they were surrounded by temptation when you've lived with control all your life and suddenly there is no one to tell you to stop, you can't help but do whatever you want." – public comment

Living experience of adults with PKU

Untreated or late-treated PKU

- “It is likely that sapropterin would have advantages for responsive individuals with untreated PKU or late treated PKU with care needs. Vernon (2010) records treating a 46-year-old man with untreated PKU with severe mental retardation and behavioural problems. On sapropterin his Phe levels reduced from 1,255 µmol/L on an unrestricted diet to 308 µmol/L. Carers noted significant behavioural improvements and indicated care needs lessened. The patient was able to have increased social interactions, and for the first time in his life was able to take a holiday with the other residents in his facility.” – patient expert comment
- “The literature suggests there are barriers to the introduction of a protein restricted diet with patients with care needs. Many patients with untreated or late treated PKU have rigid behaviours and resist change. I am also aware that care arrangements themselves can be a barrier to a strict PKU diet. Hospitals frequently are unable to provide low phenylalanine diets. Care homes or domiciliary care will also have difficulties administering the diet; which are likely to be more problematic than for parental carers – for example, the high numbers of staff who may have responsibility for supervising the diet of an individual, reliance on external caterers, staff turnover, possibly (in some cases) a lack of motivation to handle a difficult task.” – patient expert comment

Living experience of adults with PKU

Comorbidities (1)

- “I am aware of patients with early treated PKU who have learning disabilities or PKU related cognitive problems. These issues typically have an impact on whether the individual is able to manage the low phenylalanine diet independently. I am aware of people with PKU in the community who have problems like intense anxiety or problems with executive functioning which is a barrier to them being to getting a new referral to a metabolic clinic and turning up to the appointment.” – patient expert comment
- “I have a PhD, but it took me an extra year, which my GP signed off because of my anxiety, which was caused by trying to manage my diet and such a significant project as a thesis, as well as just try to live and grow as a young person!!” – public comment
- “When I turned 16 years old, I got told by the dietitian that it was safe for me to come off the diet, so I did. Although I didn't eat meat, eggs or dairy I had everything else just so I can fit in. As my brother and I were on Calogen [high energy fat emulsion drink] for all those years no dietitian told us how many calories was in it. So, we were having it in our tea, cereal and the odd milkshakes, this led to our weight to shoot up which made myself to have more issues with confidence and self-esteem.” – public comment

Living experience of adults with PKU

Comorbidities (2)

- “I would draw attention to a paper by Trefz et al (2019) which reported adults with PKU as compared to age matched controls has higher rates of depression, ischaemic heart disease, asthma, COPD, dizziness, diabetes mellitus, gastroenteritis/colitis, stress and adjustment disorders and acquired limb deformities. Of note only <1.3% were receiving sapropterin and 13.8% dietary amino acid supplement… A further contribution to overall health is the constraints of a restricted diet on exercise. It is difficult to achieve satiety on a low protein diet which means many adults report high levels of fatigue before and after exercise. Hence achieving a healthy lifestyle is limited and this may at least in part account for the higher rates of comorbidity reported such as diabetes mellitus and ischaemic heart disease.” – public comment

Caregiver quality of life - adults

- Caregivers of people with PKU experience mental health issues because of the complexity of managing PKU diet and PKU symptoms

Caregiver quality of life - adults

High burden of care

- “The guidance fails to account for care needs or carer disutility associated with adults in its costs modelling and this is a significant failing.” – patient expert comment
- The statement at paragraph 3.5 does not adequately describe that many adult patients are dependent on others to help them manage either their dietary treatment or the impairments they have as a result of PKU. NICE has not taken into account the effect that PKU has on family members that help manage PKU symptoms or PKU treatments.” – patient expert comment
- “I was incredibly lucky my mum worked in banking and then in the citizens advice bureau so could understand what help she could get, getting the benefits and tax credits needed to work part time so she could be there to support me through school with my diet and still bring in an income. I wonder how many people don’t know how to find the right help. What if an adult with PKU had to go through an experience such as losing their job, getting a divorce, having a health crisis unrelated to PKU, a family death, an abusive relationship; anything that means their world was changed forever, how could they go through that, as well as manage the extremely complex PKU diet?” – public comment

Discussion point 5 – Factors not included in the model

- A number of factors have been raised during consultation that people would like taken account of in the cost effectiveness analyses for adults.
- These include:
  - Long-term comorbidities in adults and future health care costs avoided
  - Carer's quality of life
- However, the company use a decision tree model with a 1-year time horizon to estimate the cost effectiveness of sapropterin plus a protein-restricted diet compared with protein-restricted diet alone, therefore it is not possible to include these in the current model.
- Is there a group of adults that committee have underestimated the benefits of sapropterin in?
- Committee aware of the extent of additional care provided to children with PKU by their families. To what extent is care giving provided in adults?
- Committee need to consider the different groups of adults being discussed:
  - Adults who have already sustained brain damage e.g. because of late-treated or not treated PKU, moved to UK from countries without PKU screening programmes or discontinued PKU diet in childhood based on previous clinical recommendations
  - Adults who have not sustained brain damage from PKU as a child
  - Adults with learning disabilities not related to PKU

Maternal PKU syndrome

- Women who are trying to conceive find achieving target blood Phe levels for pregnancy very difficult using only protein-restricted diet because of the much stricter levels than what they are normally used to.
  - Difficulty arises from having to maintain very low Phe levels on diet for long periods of time.
- Women feel extreme fear, shame and guilt about getting pregnant (whether planned or not) because of the risks of high blood Phe levels to the unborn child.
  - Women frequently completely forgo having intimate or sexual relationships for fear of accidentally becoming pregnant and harming their unborn child.
- The effects of high Phe levels on the unborn child and the costs associated with maternal PKU syndrome have not been included in the model.
- Current NHS policy for pregnant women with PKU is not appropriate and aims to prevent maternal PKU syndrome too late, after the damage is likely already done.

Maternal PKU syndrome

Challenges maintaining very low Phe levels (1)

- “Women with PKU can find the process of “pre-con” incredibly hard. The process of maintaining ultra low levels requires a huge effort. Women have to monitor blood levels several times a week, requiring contact with their metabolic team. It must create immense pressure to conceive swiftly, but life is not always like this. There is a practice – recommended in the European Guidelines – to refer women to a fertility specialist early if they fail to conceive quickly. I am aware this happens in some clinics in the UK but not universally so. However, this will not necessarily reduce the stress of the situation.” – clinical expert comment
- “The burden of a low protein diet during pregnancy is extremely high. The diet is required to be restricted even further to significantly reduce blood Phe concentrations to 120–360 µmol/L (van Wedberg et al 2017; compared to 600 µmol/L normally). If pregnancy is difficult and is complicated by illness such as morning sickness or gastroesophageal reflux or gestational diabetes maintaining these strict Phe blood concentrations can become close to impossible. Inadequate calorie intake secondary to nausea and vomiting is often contributory to catabolism causing dangerously high Phe levels.” – public comment

Maternal PKU syndrome

Challenges maintaining very low Phe levels (2)

- "It is unknown how long a woman with PKU would take to become pregnant. Women on a pre-conception diet that may have conditions such as PCOS or endometriosis, may take longer to become pregnant. Therefore, some women with PKU have to endure a more protracted length of time on a highly restricted diet. Potentially, some women may not be able to manage such a long course of time and not become mothers." – patient expert comment
- "NICE has not taken into account the experiences of women with PKU who have gone through the pre-conception diet and a pregnancy. This is a time when hormonal changes and other health changes due to pregnancy make the diet extra difficult. It is also a time which can result in severe illness that makes the diet extremely difficult both mentally and physically, potentially raising Phe levels and also making the experience traumatic for the woman." – public comment
- "Many women may become pregnant without properly engaging on pre-conception and present for metabolic care as swiftly as possible, but the foetus will have been exposed to high phenylalanine levels at a crucial stage of pregnancy. Only half of PKU pregnancies follow the "textbook" plan for managing PKU in pregnancy."

Maternal PKU syndrome

Challenges maintaining very low Phe levels (3)

- “I want to highlight the phrase before conception. Out of interest, I just put into google “how long does the average couple take to conceive a child” and it comes up with the NHS website saying it can take someone aged 19 to 26 – 92% will conceive after 1 year and 98% after 2 years. So, this is saying that conception can potentially take up to 1-2 years at least. That means if I want to have a child, I could have to be on an even more limited diet then I already am for up to 2 years at least and that’s as long as either myself or my husband has no fertility issues, which of course are not known until you start trying for children.
- 1-2 YEARS of being on basically no protein, having to wholly depend on prescription food and blood levels, being constantly vigilant on diet otherwise I risk my own unborn child! As well as again, having to have a full-time job, run a household etc. and all doing this with the stress of trying to conceive, which can add to fertility issues. This is the kind of stress every women has and knows that they have to go through to have a child and that’s BEFORE THE PREGANCY EVEN BEGINS.” – public comment
- To expect a pregnant woman to manage on 1 or 0 exchanges (what pregnant ladies will have to do to protect the growing foetus from the detrimental birth defects that PKU causes) is unbelievable when sapropterin will make a huge difference.” – public comment

Maternal PKU syndrome

Fear of accidental pregnancy (1)

- “I know she [adult woman with PKU] struggles with romantic relationships. Although she has a high sex drive, she is very hesitant about having sexual relationships because she is scared of becoming pregnant and having to deal with the challenges of pregnancy with PKU and the possibility of having to raise a child with PKU also. Dating is a hugely stressful thing for her because it is so loaded, and I can see it causes her great emotional turmoil.” – public comment
- “Personally, I am still unaware of what happens during the pregnancy itself, as this isn’t made clear until you decide to have a child, I don’t know why but I have spoken to many women with PKU and we all have the same story to share, that we were all warned by our consultants the dangers of unplanned pregnancies, the problem is we were all told for some of us from the age of 11! I remember having that conversation and I wasn’t even interested in makeup, never mind boys. But the tactic for years seems to be a fear tactic into getting women to not have unplanned pregnancies, warning of the risks and damages that can happen to their unborn foetus. This is because there is no other option for PKU women other than just an even stricter diet and fear. ” – public comment
- “The rate of unplanned pregnancy for women with PKU is the same as the general population. Women with PKU have the right to have sex and the right to have their reproductive rights supported in a non-discriminatory way. ” – patient expert comment

Maternal PKU syndrome

Fear of accidental pregnancy (2)

- “Discussion about having children with disabilities or problems linked to PKU is very difficult even within the PKU community. It can be difficult to acknowledge or discuss as women can feel guilt or shame.” – patient expert comment
- “I have known since I was a little girl that having a family of my own was something incredibly important to me. I am now coming to a stage in my life where I want to think about this seriously. I am so scared. I am so angry that I cannot look to my future and be excited about the possibility of having a family of my own because of my PKU. It fills me with dread, the idea that I could permanently damage an unborn child due to not doing the diet perfectly. Why are women like me put in this position? Who would want that for their sister, daughter, niece, granddaughter? Everything that I suffer my family also suffers.” – public comment
- “It’s just simply upsetting that the joy of creating life is taken away from us because it is such a terrifying idea that we could accidently poison our own child; that our inability to control such a restricting diet could result in miscarriage or an abortion because the alternative is too horrible to think about. The benefits of Kuvan for a potential mother, the chance to have potentially more protein intake and therefore the chance to have more freedom while pregnant can only have a positive impact on the unborn child as at the moment there is no choice, there is no other option than just fear.” – public comment

Maternal PKU syndrome

Fear of accidental pregnancy (3)

- “I have spoken to many young women who are extremely emotional about the prospect of becoming pregnant. They are tearful and worried and sometimes express guilt. In the NSPKU survey it was very difficult to read that some women reported (anonymously) that these fears impacted their relationships and ability to have a sexual relationship.” patient expert comment
- “It is my view that women should have access to sapropterin through their reproductive years. This will encourage women to have close ongoing relationships with their metabolic team, where women can be honest and supported to make educated choices about their sexual behaviour and plans to start a family. Maintaining good metabolic control in young women will reduce risk factors for unplanned pregnancy. Easy access to sapropterin prior to conception would make “pre-con” adherence less onerous and in my view would increase the number of women who conceive with controlled levels. I do not believe that this is a contentious view, for example the NHS England policy accepted that sapropterin makes it easier to sustain low levels, thus improving adherence and then outcomes “the diet becomes more manageable, thus improving dietary adherence.” – patient expert comment

Maternal PKU syndrome

Effects and costs of maternal PKU syndrome (1)

- "In the peer reviewed publication from the NSPKU survey 73% of women (n= 300) expressed concerns, fears and distress about pregnancy. 60% were concerned about harm they may cause to a baby, 54% had anxiety about their ability to maintain blood Phe within target, and 48% feared unplanned pregnancy. Some were concerned that it may be unsafe to have a baby as a woman with PKU (39%, n=107); some worried about their parenting skills (16%, n=43), and women even described how they avoided sexual relations.

  8% of women were too embarrassed to discuss pregnancy in clinic; 9% said they had a pregnancy termination due to PKU, 14% had a miscarriage and 8% had more than one miscarriage.

  In the post-natal period, of 93 women, 48% had low mood or sadness, 41% were depressed, 25% felt unable to cope, 33% said they could not care for their PKU as well as their baby, 14% (struggled with childcare needs and 4% worried they might hurt themselves or their baby. 14% thought that child health or developmental problems were linked to PKU." - patient organisation comment

Maternal PKU syndrome

Effects and costs of maternal PKU syndrome (2)

- "Children born to women who have PAH deficiency on unrestricted diets have a 92% risk of developmental delays, a 73% risk of microcephaly, and a 12% risk of congenital heart defects as well as growth delay and seizures" – patient expert comment
- "In the UK, there is no current registry describing child/foetal outcome following maternal PKU pregnancy. However, in 2008, Maillot et al conducted a retrospective review of outcomes in 105 children born to mothers with PKU in the UK. They found that IQ and developmental quotient at age 1 and age 8 were higher in children whose mothers started a low phenylalanine diet before pregnancy compared with those whose mothers started the diet after pregnancy began, at a mean gestational age of 10 weeks. Starting the diet before the beginning of pregnancy also reduced the risk of congenital heart disease (0% for the prior-to-pregnancy diet group vs. 12.5% for the group initiating diet 10 weeks after pregnancy began)." – clinical expert comment
- "The consequential costs of a baby born with maternal phenylketonuria syndrome are difficult to calculate but must surely be much higher than the cost of using sapropterin as first line medication through pregnancy." – public comment

Maternal PKU syndrome

Current NHS policy too late (1)

- “The idea that a pregnant lady has to have unacceptable Phe levels before being able to access Sapropterin is unethical and puts an unborn child at risk.” – patient expert comment
- “There is a current NHS policy that suggests that sapropterin can be prescribed only when women demonstrate they are unable to achieve lower blood phenylalanine levels in pregnancy. At this point women may be several weeks pregnant and no prior BH4 responsive test will have been conducted. This policy is only allowing sapropterin to be being used as a type of ‘rescue therapy’ when the clinical situation is particularly difficult and BH4 responsiveness has not been proven. This is inappropriate and this practice will not demonstrate the full benefit of sapropterin. BH4 responsive women will gain most benefit from sapropterin if it is used during the preconception phase enabling them to cope better with their diet therapy as previously explained. ” clinical expert comment
- “No country in the world has a Maternal PKU policy like the one adopted by NHS England. Nobody thinks its “optimal”, but nobody has ever taken the step of replacing it with an “optimal” policy. NICE has a duty to women with PKU to resolve this.” – patient expert comment

Maternal PKU syndrome

Current NHS policy too late (2)

- “The NHS policy on maternal PKU is a disgrace. NHS England made a policy for maternal PKU in 2013 which said they would collect and audit data about women, pregnancy and PKU. Yet they failed to collect any data. They also said they would review the policy – but yet they failed to review it. The policy is not working, and no women are being funded for Kuvan in pregnancy. NICE have done nothing to improve this. It is a known tragedy within the PKU community that babies are being born to mothers with PKU with birth defects such as learning difficulties. This is a national scandal. It is very difficult for people to admit, and there is great shame involved.” – public comment

Company comments from consultation on pregnancy (1)

- UK clinical experts estimate that there are approximately 50 to 60 PKU pregnancies per annum in the whole of UK. Of these pregnancies, it is estimated that the number of pregnant patients who will be in clinic and responsive is approximately 10 per annum. These patients might also require sapropterin treatment only for 6 to 9 months. The UK clinical experts have also confirmed that Phe tolerance increases as the foetus grows and starts to metabolise Phe itself which enables mothers to take more natural protein. In comparison to the life-time costs that would be associated with managing a child with PKU Syndrome, offering the option of sapropterin to pregnant PKU patients would result in negligible overall budget impact.
- PKUMOMS, the PKU in the Maternal Phenylketonuria Observational Program is a sub- registry of PKUDOS with two data cuts, in June 2013 and December 2018.
  - [redacted]

Company comments from consultation on pregnancy (2)

- The following birth outcome data were available for the December 2018 data-cut (reported as adverse event data):
  - [redacted]
  - [redacted]
- [redacted]
- Additional publications further state that sapropterin use in pregnant woman leads to better blood Phe control and increased Phe tolerance and offspring were all normal babies with normal birth measurements and outcomes. International best practice guideline (Muntau 2019), also recommends sapropterin response testing for pregnant woman with PKU.

Discussion point 6 – How to take account of risks in pregnancy and harm to the unborn child?

- Committee sought additional evidence on this group noting the potential huge benefits to the unborn child if women could stabilise their Phe levels whilst pregnant and/or at preconception.
- The company provided some clinical data from the registries.
- The company presents a cost effectiveness analysis for women of child-bearing age however this is difficult to define as not all these women will/want/can have a child and therefore a recommendation for this group would be discriminatory to men of the same age.
- The current model does not allow scenarios around women trying to conceive or women who are pregnant to be modelled.
- No cost effectiveness analyses have been presented for this group for committee to be able to base a decision on.
- NHSE's policy for pregnant women is still in place.
- What evidence is available for NICE or NHSE consider this group further?

Company ICER for women of child bearing age

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

Age	Symptom severity	Sapropterin dose	Annual incremental cost	QALY gain	ICER (£/QALY gained)
Woman of child-bearing age	Mild	12.5 mg/kg	[redacted]	0.49	[redacted]
	Moderate		[redacted]	0.44	[redacted]
	Severe		[redacted]	0.52	[redacted]

- Company included utility gains for for women of child-bearing age ([redacted]) receiving sapropterin in addition to the utility from reductions in PKU symptoms and protein-restricted diet.

Committee considerations

The additional utility gains modelled by the company for all women of childbearing age are not supported by evidence.

Sapropterin response definition

- “Definitions of sapropterin responsiveness and the methodology for testing sapropterin responsiveness are highly variable. It is important that a robust and practical protocol for testing responsiveness is adopted as part of this guidance – lack of such guidance may result in patients being inappropriately labelled as responsive (thus reducing cost effectiveness) and significant inequity of access.” – clinical expert comment
- “I have concerns about the lack of clear criteria concerning sapropterin responsiveness and the lack of definition of what constitutes a satisfactory response to treatment. One of the major issues in using sapropterin to treat PKU is that it has different effects in different patients. It is important to precisely define which patients are to be considered responsive to sapropterin. This involves describing the method of testing as well as what constitutes an adequate response in terms of lowering phenylalanine and/or increasing natural protein intake. Sapropterin is used as an adjunct to diet. Dietary treatment on its own can be used to achieve target phenylalanine levels in all patients, although this can be very challenging. Therefore, for different patients the goals of adding sapropterin to dietary treatment are different. For some, the goal will be to reduce phenylalanine levels into the normal range whilst for the majority, the goal will be to allow patients to maintain target phenylalanine levels with less dietary restriction. Because of this it is also very important to define criteria for what constitutes a satisfactory long-term response to sapropterin.” – clinical expert comment

Discussion point 7 – Comments outside of the remit of this appraisal

- A technology appraisal considers the clinical and cost effectiveness of a technology within its marketing authorisation.
- Some comments received are outside the remit of an appraisal and are more in line with what a guideline would cover, such as:
  - The methods and responsiveness of sapropterin testing
  - Implementation of stopping rule between child and adult services

Sapropterin off patent and generics

- “What I do not understand is why this study is only examining BioMarin Kuvan and not the generics that have started to be produced since October 2020 when the BioMarin patent ran out, from pharmaceutical companies such as Endo in Ireland.” – NSPKU forum
- “Kuvan, or rather sapropterin, is no longer in patent and cheaper, generic versions are available. Why were these cheaper options not considered in the cost-effectiveness for this draft guidance?” – NSPKU forum
- “With a "generic" product now expected, which will be cheaper has Kuvan, can we expect this revised costing to be considered and the recommendations updated once this now product is launched?”- web comment
- “Please review this again soon due to the patent running out for the branded product Kuvan, there will be other products on the market very soon and the PKU community do not deserve to wait another 3-4 years for medication which other countries have had access to for 12 years.” NSPKU forum

Additional company comments from consultation (1)

- With regard to the recommendation of sapropterin limited only to phenylketonuria (PKU) patients that are under 18 years of age, BioMarin would like to state that all PKU patients, responding to treatment, could benefit from the sapropterin treatment.
- Page 3, the ACD states that *"there is no clinical trial or registry evidence to show whether sapropterin reduces the need for a protein-restricted diet or how it affects quality of life".*
  - There are numerous publications showing that sapropterin treatment contributes to the decrease of the use of protein supplements.
  - Furthermore, the long-term PKU registries, KAMPER in Europe and PKUDOS in the US, also shows that patients receiving sapropterin experience decrease in their blood phenylalanine (Phe) levels while their natural protein intake increases.
  - The above data has been corroborated by a panel of UK clinical experts that supported a minimum of 50% reduction in the use of protein supplements, potentially reaching 100% in highly responsive patients.
- The company would like to state that brain development continues up to the age of 25, thus adolescence and early adulthood are also critical periods for brain development, education and social development. Furthermore, it has been widely demonstrated that adolescence and early adulthood are periods when Phe control becomes problematic.

Additional company comments from consultation (2)

- Page 6, ACD states that “Clinical experts estimated that 10% to 20% of patients struggle to maintain control of blood Phe levels”. Data show that adherence to a Phe-restricted diet is extremely challenging with as many as 75% of adolescents being unable to keep their blood Phe levels within the recommended target range. (Walter 2002). US study shows 40% of patients aged 13-17 years old had Phe levels higher than 360 µmol/L.
- Page 6, ACD states *“..no strict guidelines or target Phe levels used in clinical practice good control of blood Phe levels (below 200 micromoles per litre) should be maintained if possible.”* It stated in the 2017 EU Guidelines that pregnant PKU patients should maintain their Phe levels between 120 to 360 micromol/L (van Spronsen 2017) and UK clinical experts follow the European PKU guidelines.
- ACD states that *“the model time horizon is not long enough to capture long-term brain damage in people with PKU and the model is not appropriate to capture the effects of PKU in pregnancy”.* The company would like to state that owing to the teratogenic effects on children born to mothers with PKU, the model included an additional utility gain of [redacted] that sapropterin can potentially bring. This was presented to the Committee in the decision tree model.
- ACD states that *“the ERG advised that the utility reductions may be double counted, because the reductions were already captured for different PKU symptom states”.* The company would like to clarify that utility reductions have not been double counted. The health state vignettes that were presented to the general population in Sweden and clinical experts in England, did not include a description for intellectual disability and IQ deficits, hence inclusion of these in the decision tree model is not double counting.

Additional company comments from consultation (3)

- ACD states that “the committee concluded that escalation above the dose of 10 mg/kg for children and 12.5 mg/kg for adults would have a significant effect on the cost effectiveness of the treatment”. The company would like to state that in the ERG model that was presented to the committee, dose escalation from 10 mg/kg to 12.7 mg/kg had limited impact.

Age	Mean dose	Mean cost per day	Incremental daily cost	Annual incremental cost	Symptom severity	QALY incremental gain	ICER per QALY gained
0-17 years	10 mg/kg	[redacted]	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	[redacted]	[redacted]	Severe	0.145	[redacted]
	12.7 mg/kg	[redacted]	[redacted]	[redacted]	Mild	0.130	[redacted]
		[redacted]	[redacted]	[redacted]	Moderate	0.134	[redacted]
		[redacted]	[redacted]	[redacted]	Severe	0.145	[redacted]

Company base case ICERs *(ERG corrected algorithm errors [adults and women of child-bearing age])*

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]	0.20	[redacted]
	Severe		[redacted]	0.30	[redacted]
Woman of child-bearing age	Mild	12.5 mg/kg	[redacted]	0.49	[redacted]
	Moderate		[redacted]	0.45	[redacted]
	Severe		[redacted]	0.55	[redacted]

ERG alternative cost-effectiveness results (Committee's preferred scenario)

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]

ERG comments on the company response to ACD were what had been said previously.

Key discussion points

- Is it unreasonable for treatment to stop at 18 years of age?
- Is it unreasonable to recommend a dose of up to 10mg/kg for children?
- Has the due regard been given to the need to eliminate discrimination?
- What are the risks of uncontrolled Phe in adults?
- Are there additional factors (such as comorbidities and caregiver quality of life) that need to be accounted for in the cost effectiveness analysis for some adults?
- How to take account of risks in pregnancy and harm to the unborn child?