MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
28-29 July 2020

Agenda Item No	3.1
National Programme	Women and Children
Clinical Reference Group	Metabolic Medicine
URN	1840

Title
Interim Clinical Commissioning Policy: Sapropterin for Phenylketonuria

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative priority

Proposition
For routine commissioning. Phenylketonuria (PKU) is a rare genetic disorder. In the disorder, a particular substance called phenylalanine (Phe) (which is found in some food proteins) cannot be broken down and accumulates in the body. Phe is extremely toxic to the brain and untreated PKU patients or those who do not follow a controlled diet have profound brain damage with a very low IQ, seizures and behavioural and social problems, other motor difficulties and autism. Sapropterin is a treatment that aims to reduce the severity of PKU, by improving the patient's ability to process Phe, reducing the level of Phe in the body. Reductions in the Phe levels allow patients more natural protein in their diet whilst protecting brain function and development. Sapropterin is taken orally. NICE are considering this intervention / indication as part of the Technology Appraisal (TA) programme. This is an interim policy statement proposition which will be superseded by the NICE decision.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes: Impact Assessment; Consultation Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	

9.	Dependency on care giver / supporting independence	
10.	Safety	This outcome looked at the number of people reporting adverse events (side effects) while taking sapropterin. Two of the studies were long-term studies giving data for up to 7 years. Across the studies the incidence of reported adverse events was high (63−100% of participants in individual studies reported at least 1 adverse event), although many were not considered related to the study treatment (6−33% of adverse events were considered sapropterin-related in individual studies). The majority of events were mild or moderate in severity, and few people withdrew from studies due to adverse events. The most frequently reported adverse events in the clinical trials included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia. A meta-analysis combining data from 4 of the studies (Qu et al. 2019) found no statistically significant differences between sapropterin and control for any adverse events assessed. These results suggest that sapropterin is well tolerated.
11.	Delivery of intervention	

No	Outcome measure	Summary from evidence review
1.	Blood phenylalanine concentration	This outcome looked at how much phenylalanine is in a person's blood. Raised phenylalanine levels are thought to result in neurotoxicity. The studies found that, people treated with sapropterin for up to 5 years had a statistically significant reduction in blood phenylalanine concentration of approximately 100 to 200 micromol/litre from baseline (Qu et al., weighted mean difference [WMD] −100.37 micromol/litre compared with control, p=0.0005; Longo et al., difference −199 micromol/litre compared with baseline, p=0.0009). Qu et al. looked at the change in blood phenylalanine concentration in people with different levels of phenylalanine in their blood at baseline. The study found there was no statistically significant difference between sapropterin and placebo or phenylalanine restricted diet only in people with less than 600 micromol/litre of phenylalanine in their blood at baseline (WMD

		−7.75 micromol/litre, p=0.84). By contrast, in people with at least 600 micromol/litre of phenylalanine at baseline, sapropterin statistically significantly reduced blood phenylalanine concentration by about 200 micromol/litre within 6 weeks compared with placebo (WMD −225.31 micromol/litre, p<0.00001). However, one of the studies (Muntau et al. 2017) that included people with phenylalanine blood concentrations of less than 600 micromol/litre blood at baseline was designed to look at phenylalanine tolerance and phenylalanine blood concentrations were expected to be maintained within a range; therefore, differences in blood phenylalanine concentrations were not expected. These studies suggest that sapropterin reduces phenylalanine blood concentration (statically significant), particularly in people with high phenylalanine in their blood before treatment. Care should be taken when interpreting the results of biochemical outcomes. From this evidence review, it is not known if changes to a blood test translate to benefits in more patient-orientated outcomes, for example, cognitive functioning.
2.	Phenylalanine tolerance	This outcome looks at how much phenylalanine (from diet and supplements) a person with PKU can tolerate while keeping their blood phenylalanine levels within a predefined range (<360 micromol/litre). Qu et al. found that people treated with sapropterin for 10 to 26 weeks could tolerate approximately 20 mg/kg more phenylalanine each day compared with people on placebo or a phenylalanine-restricted diet alone (WMD 19.89 mg/kg/day, p<0.0001). Longo et al. found that this improvement was maintained at around 6 years (improvement of 197 mg/day from baseline), although no statistical analysis was reported for this outcome. These studies suggest that sapropterin increases the amount of phenylalanine a person with PKU can consume each day (statistically significant) and still keep their phenylalanine blood levels within acceptable limits. An increased phenylalanine tolerance could in theory allow a person with PKU to have a more relaxed diet containing more natural protein. However, the actual benefit of increased tolerance to patients can only be determined using patient-orientated outcomes, for example, physical growth.
3.	Blood phenylalanine concentration below 600 micromol/litre	European guidelines recommend that blood phenylalanine levels should be kept below 600 micromol/litre in people aged 12 years or more with PKU (below 360 micromol/litre in children aged under 12 years). This outcome looks at the proportion of people

		whose blood phenylalanine concentration was reduced to below 600 micromol/litre when they were treated with sapropterin. Levy et al. found that treatment reduced blood phenylalanine concentration to less than 600 micromol/litre in about half of the people in the sapropterin group at week 6, compared with less than a quarter of people in the control group (54% compared with 23% respectively, no statistical analysis). It is not reported if the difference between the groups was statistically significant or not, and caution should be used when interpreting the results of biochemical outcomes. Nevertheless, this result suggests that treatment with sapropterin may reduce phenylalanine blood concentrations to recommended levels in some people.
4.	Stability of blood phenylalanine concentrations	Poor control of PKU and variability in blood phenylalanine concentrations is associated with worse outcomes (such as cognitive function). This outcome looks at whether phenylalanine blood concentrations became more stable when people were treated with sapropterin. Blood phenylalanine concentrations varied less while people were treated with sapropterin compared with the period before they took the treatment (mean within subject variance 4.8 compared with 6.9 respectively, p=0.0017, statistically significant). This result suggests that sapropterin treatment improves the stability of blood phenylalanine concentrations. However, this is a small, observational study with many limitations. Also, it is unclear from this evidence review if changes in blood concentration translate to benefits in cognitive functioning.
5.	Natural protein intake	People with PKU should follow a strict low protein-restricted diet and take an amino acids supplement (without phenylalanine). This outcome looks at whether people who were taking sapropterin could increase their natural protein intake without their blood phenylalanine levels increasing. The amount of protein people were advised to eat increased by 230 mg/kg/day over 5 years in the sapropterin group compared with baseline (p<0.001, statistically significant). At 5 years, natural protein intake was 280 mg/kg/day higher in the sapropterin group than in the control group (p<0.001, statistically significant). This result suggests that people taking sapropterin may be able to eat more natural protein without their phenylalanine blood concentration increasing. This would mean that people with PKU could eat a more ‘normal’ diet, which is likely to be easier for

		them. However, prescribed natural protein intake was assessed in the study because too few data were available to assess true natural protein intake, and it is unknown how well people adhered to the prescribed protein intake. It is unclear from this evidence review if increasing natural protein intake translates to benefits in patient-orientated outcomes.
6.	Amino acid supplement intake	This outcome looks at whether people who were taking sapropterin could reduce the amount of amino acid supplement they were taking because they were eating more natural protein. The amount of amino acid supplement people were advised to take decreased by 670 mg/kg/day over 5 years in the sapropterin group compared with baseline ($p<0.001$, statistically significant). At 5 years, amino acid intake was 420 mg/kg/day lower in the sapropterin group than in the control group ($p=0.002$, statistically significant). These results suggest that people taking sapropterin may be able to reduce the amount of amino acid supplement that they take. This is likely to be beneficial to people with PKU because the supplements taste unpleasant. However, this result is from a small, observational study with many limitations. It is not known how well people adhered to the prescribed amino acid supplement intake, or how reducing amino acid intake translates to benefits in patient-orientated outcomes

Considerations from review by Rare Disease Advisory Group

The Rare Disease Advisory Group (RDAG) considered the following question regarding the sapropterin policy proposition:

1) What specific considerations should CPAG include when looking at this policy considering the relative rarity of the condition?

RDAG members thought that there may be a small cohort of patients who have a diagnostic delay but not many because it is one of the conditions tested during the newborn bloodspot screening programme.

2) Determine whether any aspect of the administration of the treatment should be considered a Highly Specialised Service.

RDAG members did not note any aspects of the administration of the treatment that should be considered as a Highly Specialised Service

3) Does the equality and health Inequalities impact assessment adequately take into account all aspects:

RDAG members did not note any omissions in the equality and health Inequalities impact assessment

Pharmaceutical considerations
This policy proposition recommends sapropterin for the treatment of patients with phenylketonuria. This is within its licensed indication. Sapropterin is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposition received the support of the Women and Children PoC on the 15th June 2020. The PoC recommended a number of changes which were subsequently made by the Policy Working Group.