CLINICAL PRIORITIES ADVISORY GROUP
06 and 07 November 2018

Agenda Item No	04.5
National Programme	Women and Children
Clinical Reference Group	Metabolic
URN	170103P

Title
Sapropterin for Phenylketonuria

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend the 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. NHS England considered a commissioning policy for this drug in 2014/15. The decision was not to routinely commission except for pregnant women. NICE are considering this intervention / indication as part of the Technology Appraisal (TA) programme with a decision expected August 2019. Therefore this is an interim policy statement proposition.

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 confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board 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 Operational Delivery 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 (as this is an interim policy there was no public consultation). Stakeholder Report included.
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

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. This outcome was reported in 7 studies (3 double-blind RCTs, 1 open-label RCT, 2 open-label extension studies and 1 open-label prospective study), involving a total of 564 participants. The incidence of reported adverse events was high, although 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.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
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. This outcome was reported in 3 studies (2 double-blind RCTs and 1 open-label extension study) involving a total of 214 participants. The studies found that people treated with sapropterin for up to 22 weeks had a reduction in blood phenylalanine concentrations of approximately 200 micromol/litre from baseline. This reduction is significantly higher than seen in people treated with placebo, whose phenylalanine levels remained the approximately the same after 6 weeks treatment. These studies suggest that sapropterin significantly reduces phenylalanine blood concentration. Care should be taken when interpreting the results of biochemical outcomes, as changes to a blood test may not 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 whilst keeping their blood phenylalanine levels within a

		predefined range (<360 micromol/litre). Phenylalanine tolerance was reported in 2 studies (1 double-blind RCT and 1 open-label RCT) involving a total of 101 participants. The studies found that people treated with sapropterin for 10 to 26 weeks could tolerate approximately 20-30 mg/kg more phenylalanine each day compared with people on phenylalanine restricted diet alone. These studies suggest that sapropterin significantly increases the amount of phenylalanine a person with PKU can consume each day 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.	Physical growth	This outcome looks at how fast children with PKU grew when treated with sapropterin. A number of parameters were measured for growth, including weight, height and head circumference. Most studies reported growth using Z-scores (standard score), which report how many standard deviations from the mean a measurement sits. A Z-score of 0 is equal to the mean, or the 50th percentile for growth. A Z-score of −1 is equal to 1 standard deviation below the mean, and a Z-score of +1 is equal to 1 standard deviation above the mean. Physical growth was reported in 4 studies (1 open-label RCT, 1 open-label prospective study and 2 retrospective longitudinal studies) involving a total of 225 participants. No statistically significant changes in growth were observed in any study. In Muntau et al. 2017 there was no significant difference between sapropterin and diet alone for any growth parameter, with children in both treatment arms having stable growth parameters. Longo et al. 2015 found that, at baseline children had Z-scores slightly above the 50th percentile for height, weight and head circumference (0.4, 0.4 and 0.3 respectively). These values were maintained over the 2 year follow-up, with no statistically significant difference from baseline to 2 years. Two studies by Aldámiz-Echevarría et al. (2015 and 2013) found no difference from baseline to study end (12 months and up to 5 years) for any growth parameter Z-score for either the sapropterin or the diet only group.

		These results suggest that sapropterin did not significantly increase physical growth compared with diet alone, despite children treated with sapropterin having a larger intake of natural protein.
4.	Attention deficit and hyperactivity disorder (ADHD) symptoms	This outcome looks at symptoms of ADHD in adults and children with PKU. Symptoms were measured using the ADHD Rating Scale (ADHD RS) in children and the Adult Self-Report Scale (ASRS) in adults. This outcome was reported in 1 double-blind RCT involving 38 participants with ADHD symptoms at baseline. After 13 weeks treatment there was no significant difference in change from baseline in ADHD RS/ASRS Total Score for sapropterin compared with placebo (between group difference −4.2, 95% CI −8.9 to 0.6, p=0.085). Analysis of the ADHD RS/ASRS subscales-hyperactivity/impulsivity and inattention found no significant difference between treatments in the hyperactivity/impulsivity subscale (between group difference −1.0, 95% CI −3.4 to 1.4, p=0.396), and a significant difference in favour of sapropterin in the inattention subscale (between group difference −3.4, 95% CI −6.6 to −0.2, p=0.036). These results suggest that sapropterin does not improve overall ADHD symptoms compared with diet alone. Inattention symptoms of ADHD may be improved by sapropterin, although care should be taken when interpreting the positive benefits of secondary outcomes in studies that failed to demonstrate a significant result for the primary outcome.
5.	Executive function	This outcome looks at executive functions, a set of cognitive processes that control behaviour, and are needed for basic cognitive processes including paying attention, planning/organisation and managing tasks. Impaired executive function has been reported in people with PKU. Executive function was measured using the Global Executive Composite (GEC), Metacognition Index (MI) and Behaviour Regulation Index (BRI) scores from the Behaviour Rating Inventory of Executive Function (BRIEF). Scores for each BRIEF domain were reported as standard T-scores, and were compared to normative tables that provide T-scores, percentiles and 90% CIs by age and gender. Standard T-scores have a mean of 50 points. Higher T-scores indicate poorer executive function, with T-scores >65 typically considered clinically significant, but T-scores >60 on BRIEF self-reports may warrant clinical interpretation. Executive function was reported in 1 double-blind RCT involving 118 participants.

		There was no significant difference in any measure of executive function for adults treated with sapropterin compared with placebo. Children and adolescents treated with sapropterin had significantly improved GEC (treatment difference −4.1, 95% CI −7.9 to −0.3, p=0.034) and MI (treatment difference −4.4, 95% CI −8.5 to −0.2, p=0.038) scores compared with placebo. An improvement in BRI score was also observed in children and adolescents, however difference between sapropterin and placebo was not statistically significant (−3.4, 95% CI −6.8 to 0.0, p=0.053). These results suggest that children and adolescents treated with sapropterin may have improvements in elements of executive function. The authors note that improvements were driven by better scores on the MI scale, which includes initiation, working memory, planning/organising, organizing materials, and monitoring. The results also suggest that initiating sapropterin therapy in adults is unlikely to improve executive function. These results should be interpreted with caution as the double-blind phase of the trial was short (13 weeks), and the long-term effect of sapropterin on executive function is not known. It is also not clear why the results are reported separately by age group (rather than for the whole study population). Splitting the study population does not appear to be a predefined part of the outcome, and also reduces the power.
6.	Neuro-cognitive function / Intelligence	This outcome looked at neuro-cognitive functioning / intelligence in children with PKU, reported as Full Scale Intelligence Quotient (FSIQ) score. The scoring tool used was dependent on the age of the child. This outcome was reported in 1 open-label, prospective study involving 65 participants. The study reported that at baseline the average FSIQ score was not significantly different to the population average of 100 (numerical results not reported). Over the 2 year follow-up there was no significant change in FSIQ score, leading the authors to conclude that sapropterin preserved neurocognitive function. These results suggest that children treated with sapropterin for 2 years did not have a statistically significant reduction in neuro-cognitive function. These results should be interpreted with caution, since

		there was no control group it is not clear whether people treated with diet alone would have a significant reduction in neuro-cognitive function during the 2 year study period. The study is further limited by the authors not reporting numerical results for all neuro-cognitive scoring tools.
7.	Neuro-motor development	This outcome looked at neuro-motor development, covering 4 developmental milestones: personal-social function, language, fine motor skills and gross motor skills. This outcome was reported in 1 open-label RCT involving 56 participants. At week 26 there was no significant difference between sapropterin and diet only for any of the developmental milestones. Results only presented diagrammatically. These results suggest that sapropterin does not improve neuro-motor development compared with diet alone. These results should be interpreted with caution as the study only had a 6 month follow-up period, the longer term effects on development are not reported. It is also not clear from the published paper how the individual developmental milestones were assessed, and whether validated methods were used.
8.	Global function	This outcome looks at global functioning, assessed using the Clinical Global Impression of Improvement (CGI-I) scale. The CGI-I scale involves a person's clinician scoring how much their condition has changed from baseline. The scale is scored from 1 (very much improved) to 7 (very much worse). Global function was reported in 1 double-blind RCT involving 118 participants. There was no significant difference in the proportion of people 'much improved' (score 2) or 'very much improved' (score 1) in the sapropterin group (21.7%) compared with the placebo group (26.3%, p=0.670). These results suggest that sapropterin does not improve global function (as assessed by a clinician) compared with placebo. These results should be interpreted with caution as the double-blind phase of the trial was short (13 weeks), and the long-term effect of sapropterin on global function is not known.
9.	Health-related quality of life	This outcome looked at the impact of sapropterin treatment on quality of life. This outcome was reported in 2 prospective observational studies involving a total of

		155 participants. Both studies investigated patient quality of life, with Feldmann et al. (2017) also reporting on parent quality of life. Different scoring tools were used to assess quality of life. The studies report conflicting results, with no improvements in quality of life observed for children with PKU or their parents in the study by Feldmann et al. In Cazzorla et al., people with mild PKU treated with sapropterin reported significantly better quality of life compared with people with classical PKU treated with diet alone. It is not clear whether sapropterin improves quality of life in children and adults with PKU.

Considerations from review by Rare Disease Advisory Group
Not applicable.

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
The proposal receives the full support of Women and Children's Programme of Care on the 22nd October 2018.