SPECIALISED COMMISSIONING - CLINICAL EVIDENCE EVALUATION CRITERIA FOR CLINICAL COMMISSIONING POLICY PROPOSITION

URN: 1840
TITLE: Sapropterin for phenylketonuria
CRG: Metabolic Disorders
NPOC: Women and Children
Lead: [redacted]
Date: 18 September 2018

This policy is being considered for:	For routine commissioning	X	Not for routine commissioning	
Is the population described in the policy similar to that in the evidence reviewed, including subgroups?	Yes. Clinical panel noted that the market authorisation requires the trail of sapropterin with a ≥30 percent reduction in blood phenylalanine levels achieved by the end of one month of treatment whilst dietary phenylalanine intake is maintained at a constant level. This is reflected in the policy. Sapropterin is unfortunately not effective in a significant proportion of patients because only people with PKU who have residual phenylalanine hydroxylase activity will respond to treatment with sapropterin. The studies report results for patients who are responsive to sapropterin.			
Is the intervention described in the policy similar to the intervention for which evidence is presented in the evidence review?	Yes. Sapropterin in sapropterin responsive children and adults with PKU.			
Are the comparators in the evidence reviewed plausible clinical alternatives within the NHS and are they suitable for informing policy development?	Yes. The comparator is dietary management. Panel noted that a low diet excludes virtually all natural protein and synthetic protein is substituted which is unpleasant. Adherence to a low phenylalanine diet is difficult.			
Are the clinical benefits described in the evidence review likely to apply to the eligible population and/or subgroups in the policy?	Yes. Reduction in plasma phenylalanine levels were demonstrated; in patients not adhering to a low phenylalanine diet with a statistically significant reduction in blood phenylalanine concentrations of approximately 200 micromol/litre from baseline (approximately 25% relative reduction); in children with well controlled PKU on a low phenylalanine diet sapropterin resulted in a 135 micromol/litre reduction in blood phenylalanine concentrations.			

	A less restrictive diet could be adopted with increased phenylalanine tolerance by 20 to 30 mg/kg/day compared with diet alone. A small proportion of patients may be able to eat an unrestricted diet. [Post meeting note – some foods such as some fruit and vegetables low in protein contain little phenylalanine; i.e. 50g of carrots contain 10mg of phenylalanine. This contrasts with a 55g boiled egg (340 mg phenylalanine); 25g slice of wholemeal bread (100 mg phenylalanine) and a 120g of stewed mince (1200mg phenylalanine).] Panel requested that some additional information on the dietary advantages of increasing phenylalanine consumption by 20 to 30mg/kg/day would be helpful. This can be added in parallel with stakeholder testing. Panel noted that objective measures of clinical benefit were generally limited in the sapropterin responsive patients included in the studies. . Panel noted that sapropterin did not result in improved growth in children from baseline to up to 2 years and no improvement in overall attention deficit hyperactivity disorder (ADHD) symptoms in adults and children. There was also no significant difference in neuro-motor development from baseline to 26 weeks in children treated with sapropterin. One study reported no significant decline in IQ from baseline to 2 years in children with PKU treated with sapropterin. However, this was an observational study with no control group. Panel noted that there was no significant improvements in clinician assessed global functioning reported for adults or children with PKU receiving sapropterin. Health-related quality of life was poorly reported, with 2 observational studies reporting conflicting results. Treatment did improve some symptoms of inattention. Treatment also resulted in significant improvements in some elements of executive functioning in children (but not adults).
Are the clinical harms described in the evidence review likely to apply to the eligible and /or ineligible population and/or subgroups in the policy?	Yes. Adverse effects are quite common, but discontinuation rates are relatively low.
The Panel should provide advice on matters relating to the	Panel noted that the studies and the policy restrict use to sapropterin responsive patients and note that there remains a significant population of people with PKU

<table>
<tr><td>evidence base and policy development and prioritisation. Advice may cover:
• Balance between benefits and harms
• Quality and uncertainty in the evidence base
• Challenges in the clinical interpretation and applicability of policy in clinical practice
• Challenges in ensuring policy is applied appropriately
• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review.</td><td colspan="3">unlikely to benefit from sapropterin.

Panel noted the positive effect (reduction) in blood levels of phenylalanine, probably greater in patients with poor adherence to a low phenylalanine diet. It was disappointing that these biochemical markers of effectiveness did not seem to be reflected in significant improvements in a number of clinical measures including growth and ADHD. There were some clinical benefits described. It is possible but uncertain, that greater benefits may emerge over longer treatment periods.

Policy Proposition to proceed to stakeholder testing and public consultation in readiness to be considered by the Clinical Priorities Advisory Group in November 2018.</td></tr>
<tr><td rowspan="5">Overall conclusion</td><td rowspan="2">This is a proposition for routine commissioning and</td><td>Should proceed for routine commissioning</td><td>X</td></tr>
<tr><td>Should be reversed and proceed as not for routine commissioning</td><td></td></tr>
<tr><td rowspan="2">This is a proposition for not routine commissioning and</td><td>Should proceed for not routine commissioning</td><td></td></tr>
<tr><td>Should be reconsidered by the PWG</td><td></td></tr>
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Report approved by:

David Black
Deputy Medical Director Specialised Services
20 September 2018