CPAG Summary Report for Clinical Panel – Sapropterin for phenylketonuria

The Benefits of the Proposition			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	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	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Blood phenylalanine concentration	Grade A	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	Grade A	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 was analysis reported for this outcome. These studies suggest that sapropterin increases the amount of phenylalanine a person with PKU can consume each day (statically 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	Grade B	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	Grade C	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	Grade C	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	Grade C	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