

**NHS England**

## **Evidence review: Sapropterin for phenylketonuria**

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The content of this evidence review was up-to-date in March 2020. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information. For details on the date the searches for evidence were conducted see the [search strategy](#).



# Key points

**Regulatory status:** Sapropterin received a marketing authorisation in 2008 and was launched in the UK in 2009. Sapropterin is licensed for treating hyperphenylalaninaemia in adults, young people and children of all ages with phenylketonuria (PKU) who are responsive to treatment with sapropterin.

Sapropterin is also licensed for treating hyperphenylalaninaemia in adults, young people and children of all ages with tetrahydrobiopterin (BH4) deficiency, although use for this indication is outside of the scope of this evidence review.

Sapropterin has an orphan medicine designation. Orphan medicines are:

- used to treat life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the European Union, or
- medicines which, for economic reasons, would be unlikely to be developed without incentives.

## Overview

This evidence summary considers the best available evidence for using sapropterin in managing PKU.

PKU is an inherited disease in which deficiency of the enzyme phenylalanine hydroxylase results in raised phenylalanine levels in the blood. Without treatment, PKU can cause brain damage, growth failure, behavioural problems and other developmental issues.

The aim of treatment in PKU is to lower phenylalanine levels to within safe limits, to try and prevent neurological damage. The [European guidelines on the management of PKU](#) recommend that children aged under 12 years should maintain a blood phenylalanine level between 120 and 360 micromol/litre, and people aged 12 years and over between 120 and 600 micromol/litre.

Only people with PKU who have residual phenylalanine hydroxylase activity will respond to treatment with sapropterin. It is essential that response to treatment is assessed, and sapropterin only continued in people whose blood phenylalanine concentration reduces by an appropriate amount (see the [sapropterin summary of product characteristics \(SPC\)](#) for more information).

This evidence review focusses on a meta-analysis ([Qu et al. 2019](#)), which includes 3 double-blind randomised controlled trials (RCTs, [Levy et al. 2007](#), [Trefz et al. 2009](#), [Burton et al. 2015](#)) and an open-label RCT ([Muntau et al. 2017](#)). The RCT by Levy et al. (2007) is also included in the evidence review because it provides evidence for an additional outcome, which is not considered in the meta-analysis. Longer-term data are provided by an open-label extension study ([Burton et al. 2011](#)) and a registry study ([Longo et al. 2015](#)). Two observational studies that report additional outcomes are also included ([Burton et al. 2010](#) and [Evers et al. 2018](#)).

Overall, the results of these studies suggest that sapropterin reduces blood phenylalanine concentrations and increases phenylalanine tolerance in adults, young people and children

with PKU, allowing people to increase the amount of natural protein in their diet. Adverse events, while relatively common were generally mild to moderate in severity and rarely resulted in treatment being stopped.

The meta-analysis by Qu et al. (2019) found that people treated with sapropterin for 3 to 6 weeks had statistically significantly lower blood phenylalanine concentrations compared with people treated with placebo or phenylalanine-restricted diet only. The results varied depending on how much phenylalanine people had in their blood when they entered the study. In people with phenylalanine blood concentrations of less than 600 micromol/litre blood at baseline, Qu et al. found there was no statistically significant difference between sapropterin and placebo or phenylalanine-restricted diet only over 4 to 6 weeks. By contrast, sapropterin statistically significantly reduced blood phenylalanine concentration by about 200 micromol/litre over 3 to 6 weeks in people with phenylalanine blood concentrations of more than 600 micromol/litre blood at baseline. 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.

A prospective registry study by Longo et al. (2015) suggests that reductions in phenylalanine blood concentrations are maintained with long-term sapropterin treatment. After 5 years, a statistically significant 199 micromol/litre improvement was seen compared with baseline.

There is no published minimal clinically important difference for blood phenylalanine concentration, although in Levy et al. (2007), after 6 weeks, more people in the sapropterin group had blood phenylalanine concentrations within limits recommended in the [European guidelines on the management of PKU](#) compared with placebo (54% compared with 23% respectively, no statistical analysis).

A small observational study ([Burton et al. 2010](#)) found that blood phenylalanine concentrations were statistically significantly more stable when people were treated with sapropterin compared with the pre-treatment period. However, from this study, it is unclear how this improvement affects patient-orientated outcomes such as cognitive function.

The meta-analysis by Qu et al. found that people taking sapropterin for 10 to 26 weeks could tolerate about 20 mg/kg more dietary phenylalanine each day compared with people treated with placebo or a phenylalanine-restricted diet only (a statistically significant difference), and the observational study by Longo et al. found that this effect was maintained long-term. After 5 to 6 years, mean dietary phenylalanine intake had increased by about 200 mg/day in Longo et al. (although no statistical analyses were reported for this outcome). These results suggest, that sapropterin may enable people with PKU to have a less restrictive diet containing more natural protein.

People treated with sapropterin in a small observational study ([Evers et al. 2018](#)) were able to increase the natural protein in their diet, and decrease the amount of amino acid supplement they took (statistically significant differences compared with baseline). However, prescribed natural protein and amino acid intake was assessed, not actual protein or amino acid intake, which would have been more difficult to measure.

No evidence was found to determine whether or not sapropterin is a cost-effective treatment option for adults or children with PKU.

Studies included in this review report on long-term safety data on sapropterin for up to 7 years. The majority of adverse events were mild or moderate in severity, and adverse events leading to withdrawal from the studies were rare. 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.

The SPC for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in  $\geq 1/10$  people treated with sapropterin. Common adverse reactions (occurring in  $\geq 1/100$  to  $< 1/10$  people treated with sapropterin) include hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

The studies included in this evidence review are of variable quality, ranging from a meta-analysis that included high quality, double-blind RCTs to low quality, retrospective observational studies. Some outcomes, such as stability of blood phenylalanine concentration, and protein intake and amino acid intake, are only reported in lower quality studies, which have many limitations affecting their application to clinical practice.

It is difficult to assess the clinical relevance of some of the outcomes discussed in this evidence review because they do not have published minimal clinically important differences. Also, results for many of the outcomes should be interpreted with caution because they are disease-orientated outcomes, such as blood test results. Evidence showing whether sapropterin improves patient-orientated outcomes, such as cognitive functioning or physical growth would be useful to help determine its place in therapy.

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## 1. Introduction

### Background and current guidance

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterised by an increase of phenylalanine in the blood and body fluids (hyperphenylalaninaemia, [Somaraju and Merrin 2015](#)).

Phenylalanine is an essential amino acid provided by protein in the diet. A small amount of phenylalanine is used for protein synthesis, with the rest hydroxylised (converted) to another amino acid called tyrosine. People with PKU have a mutation in the gene that encodes an enzyme called phenylalanine hydroxylase, the enzyme responsible for the conversion of phenylalanine to tyrosine. The reduced levels of phenylalanine hydroxylase result in an accumulation of phenylalanine in the blood. Raised phenylalanine levels can be harmful, damaging the brain. Infants with untreated PKU appear to develop normally for the first few months of life, but soon show signs of progressive encephalopathy (brain damage). Other features of untreated PKU include growth failure, microcephaly, seizures, intellectual impairment and behavioural problems (Somaraju and Merrin 2015).

PKU is a rare condition, with an incidence of approximately 1 in 10,000 in people of European family origin. PKU is 1 of the 9 diseases tested for in the [NHS newborn blood spot screening programme](#).

The [European guidelines on the management of PKU](#) were published in 2017. They state that the primary goal of treatment is normal neurocognitive and psychosocial functioning, and that blood phenylalanine concentrations is the best surrogate measure for checking this and should be monitored regularly. The guidelines recommend that children aged under 12 years should maintain a blood phenylalanine level between 120 and 360 micromol/litre, and people aged 12 years and over between 120 and 600 micromol/litre.

A phenylalanine-restricted diet is the standard treatment, designed to reduce phenylalanine levels while providing sufficient tyrosine and other nutrients needed for growth and development. This diet excludes all high protein foods (for example, meat, fish and dairy products) and requires tight control of food containing less natural protein (for example, some fruits and vegetables). Daily supplements containing amino acids are required. Such a diet is very restrictive in nature, the supplements have an unpleasant taste, and there is always a risk of nutritional deficiencies.

Phenylalanine-restricted diets may have a negative impact on a person's quality of life, and it has been reported that by early adulthood many people with PKU do not comply with their diets (Somaraju and Merrin 2015). In a questionnaire study conducted in the United States, 88% of children with PKU aged 0 to 4 years had blood phenylalanine concentrations within clinic recommended limits (which was in line with European guideline recommendations for the majority of clinics). In comparison, only 33% of adults aged over 30 years had phenylalanine levels within recommended limits ([Jurecki et al. 2017](#)). Similar results were reported by [Brown and Lichter-Konecki \(2015\)](#), who surveyed people with PKU, finding people aged 18 years or under were around 3 times more likely to keep their blood phenylalanine concentrations within recommended limits compared with older people. The study found 52% of people with PKU had difficulty in managing their condition, including adherence to dietary restrictions. A systematic review by [Enns et al. \(2010\)](#) assessed

outcome data for patients whose PKU was managed using a phenylalanine-restricted diet alone, finding sub-optimal outcomes for neurocognitive and psychosocial functioning, quality of life, brain pathology and physical growth.

A NICE Technology Appraisal has been proposed for [Sapropterin for treating phenylketonuria \(ID1475\)](#) but is suspended.

## **Product overview**

### ***Mode of action***

Tetrahydrobiopterin is a co-factor for phenylalanine hydroxylase, which is thought to enhance the activity of residual phenylalanine hydroxylase. Sapropterin is a synthetic version of naturally occurring tetrahydrobiopterin.

Only people with PKU who have residual phenylalanine hydroxylase activity will respond to treatment with sapropterin. The [sapropterin summary of product characteristics \(SPC\)](#) advises that phenylalanine levels should be checked before administering sapropterin and after 1 week of use at the recommended starting dose (10 mg/kg/day). If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels over a one month period. The SPC defines a satisfactory response as reduction in blood phenylalanine levels of 30% or more from baseline, or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. If phenylalanine levels are not reduced by this amount, treatment with sapropterin should not be continued.

### ***Regulatory status***

Sapropterin is licensed for treating hyperphenylalaninaemia in adults, young people and children of all ages with PKU who have been shown to be responsive to treatment with sapropterin.

Sapropterin is also licensed for treating hyperphenylalaninaemia in adults, young people and children of all ages with tetrahydrobiopterin (BH4) deficiency, although use for this indication is outside of the scope of this evidence review.

Sapropterin has an orphan medicine designation. Orphan medicines are:

- used to treat life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the European Union, or
- medicines which, for economic reasons, would be unlikely to be developed without incentives.

### ***Dosing information***

The starting dose of sapropterin in adults, young people and children with PKU is 10 mg/kg once daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood phenylalanine levels (SPC for sapropterin).

## 2. Methodology

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the [literature search terms](#) section for more information). The research questions for this evidence review are:

1. In people with PKU requiring treatment to control phenylalanine levels, what is the clinical effectiveness of sapropterin treatment compared to no sapropterin treatment?
2. In people with PKU requiring treatment to control phenylalanine levels, what is the safety of sapropterin treatment compared to no sapropterin treatment?
3. In people with PKU requiring treatment to control phenylalanine levels, what is the cost effectiveness of sapropterin treatment compared to no sapropterin treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from sapropterin more than the wider population of interest?

The search for evidence to support the use of sapropterin for phenylketonuria was undertaken by NICE Guidance Information Services. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on [search strategy](#) and [evidence selection](#).

The NICE [evidence summary: process guide](#) (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the [grade of evidence](#) section for more information).

## 3. Summary of included studies

This evidence review focusses on 1 meta-analysis ([Qu et al. 2019](#)), which includes 3 double-blind randomised controlled trials (RCTs, [Levy et al. 2007](#), [Trefz et al. 2009](#), [Burton et al. 2015](#)) and an open-label RCT ([Muntau et al. 2017](#)). The RCT by Levy et al. (2007) is also included in the evidence review because it provides evidence for an additional outcome, which is not considered in the meta-analysis. Longer-term data are provided by an open-label extension study ([Burton et al. 2011](#)) and a registry study ([Longo et al. 2015](#)). Two observational studies that report additional outcomes are also included ([Burton et al. 2010](#) and [Evers et al. 2018](#)).

A summary of the included studies is shown in table 1 (see the [evidence summary tables](#) for full details).

**Table 1 Summary of included studies**

Study	Population	Intervention and comparison	Primary outcome(s)
<p><a href="#">Qu et al. 2019</a></p> <p>Systematic review and meta-analysis of 4 RCTs (Levy et al. 2007, Trefz et al. 2009, Burton et al. 2015 and Muntau et al. 2017)</p>	<p>307 people with PKU (see below for details of the individual RCTs)</p> <p>Participants could be following phenylalanine-restricted diet or not.</p> <p>Baseline characteristics of the total study population were not reported. Details of the study by Levy et al. are below. Details of the studies by Trefz et al. 2009, Burton et al. 2015 and Muntau et al. 2017 are shown in table 2.</p>	<p>Sapropterin (n=162, dosage range 10–20 mg/kg/day)</p> <p>Placebo or no supplementation (n=145)</p>	<p>Change in blood phenylalanine concentration<sup>1</sup></p> <p>Change in phenylalanine tolerance<sup>1</sup></p> <p>Adverse events</p>
<p><a href="#">Levy et al. 2007</a></p> <p>Double-blind RCT in 16 centres in North America and 14 centres in Europe.</p>	<p>89 adults and children aged ≥8 years (mean age 20.4 years, 58% male) with PKU responsive to sapropterin treatment.</p> <p>Participants were not following a phenylalanine-restricted diet at baseline and were required to continue their diet unchanged throughout the study period.</p>	<p>Sapropterin 10 mg/kg/day (n=42)</p> <p>Placebo (n=47)</p>	<p>Change in blood phenylalanine concentration<sup>1</sup> from baseline to week 6</p> <p>Adverse events also reported (not primary outcome)</p>
<p><a href="#">Burton et al. 2011</a></p> <p>Open-label extension study to <a href="#">Lee et al. 2008</a> (an open-label extension study that followed Levy et al. 2007) and Trefz et al. 2009</p> <p>Conducted in 15 centres in the United States, Canada and Europe (including sites in the UK)</p>	<p>111 people (mean age 16.4 years, 60.4% male) with PKU responsive to sapropterin.</p> <p>The study had no dietary restrictions and phenylalanine intake was not monitored.</p>	<p>Sapropterin 5 mg to 20 mg/kg/day (n=111)</p> <p>No control</p>	<p>Long-term safety – adverse events up to 3 years</p>
<p><a href="#">Longo et al. 2015</a></p> <p>Prospective observational study (the PKUDOS registry) in 52 sites in the United States</p>	<p>1,189 people (age range 0 to 63 years, 8% aged &lt;4 years, 52% female) with PKU who had previously taken, were currently taking or intended to take sapropterin within 90 days</p>	<p>504 participants were continuously exposed to sapropterin following enrolment (median dose 20 mg/kg/day for a median of 4 years)</p> <p>211 participants stopped</p>	<p>Data for up to 7 years – change in blood phenylalanine concentration<sup>1</sup></p> <p>change in phenylalanine tolerance<sup>1</sup></p>

	of study enrolment.  The study did not specify any dietary restrictions.	sapropterin within 3 months (median dose 20 mg/kg/day for between 0.03 and 3 months)  Exposure to sapropterin varied among the other 474 participants and these are not discussed	adverse events
<a href="#">Burton et al. 2010</a>  Retrospective observational study in 1 centre in the United States	37 adults and children (mean age 12.6 years, 57% female) with PKU responsive to sapropterin.  Most participants were on a phenylalanine-restricted diet.	Sapropterin (mean dose 20 mg/kg/day) for at least 1 year (mean 19 months)  Compared outcomes in the periods before and after treatment initiation	Stability of blood phenylalanine levels
<a href="#">Evers et al. 2018</a>  Retrospective case-control study in 2 centres in The Netherlands	42 people (mean age 13 years, 67% female) with PKU responsive to sapropterin.  The study did not specify any dietary restrictions but all participants were regularly seen by a dietician.	21 people had been taking sapropterin (dose not reported) for at least 5.5 years  These cases were matched (by age and gender) with 21 controls who did not take sapropterin	Changes in natural protein and amino acid supplement intakes over 5 years
<sup>1</sup> There is no published minimal clinically important difference for this outcome, see the <a href="#">Results section</a> for a discussion on the clinical relevance of these results			
<b>Abbreviations:</b> PKU, phenylketonuria; PKUDOS, Phenylketonuria Demographics, Outcomes and Safety; RCT, randomised controlled trial			

**Table 2 Summary of studies included in the meta-analysis and not discussed individually in the evidence review**

<a href="#">Trefz et al. 2009</a>  Double-blind RCT in 15 centres across Europe and the United States.	45 children (mean age 7.5 years, 58% male) with PKU responsive to sapropterin treatment.  All participants were on a phenylalanine-restricted diet which was maintained throughout the study period. Starting at week 3 phenylalanine supplements were introduced.	Sapropterin 20 mg/kg/day (n=33)  Placebo (n=12)	Mean daily phenylalanine supplement tolerated over 10 weeks  Adverse events also reported (not primary outcome)
<a href="#">Burton et al. 2015</a>  Double-blind RCT in 36 centres across the United States and Canada.	118 adults and children aged 8 years and over (mean age approximately 20 years, 58% male) with PKU responsive to sapropterin.  Participants were required to continue on their current diet. The authors do not provide details on	Sapropterin (dose not reported) (n=61)  Placebo (n=57)  19 participants in each group had ADHD symptoms at baseline	Change in ADHD symptoms at 13 weeks  and  Change in global

	the diets the participants followed, although raised blood phenylalanine levels at baseline suggest that at least some people in the study were not following a strict phenylalanine-restricted diet.		function at week 13  Adverse events also reported (not primary outcome)
<a href="#">Muntau et al. 2017</a>  Open-label, RCT in 22 centres in 9 countries, (including 2 centres in the UK).	56 children aged under 4 years (mean age 21 months, 59% male) with PKU responsive to sapropterin.  All participants followed a phenylalanine-restricted diet and were required to have good phenylalanine control (between 120 and 360 micromol/litre for 4 months before screening). Participants could adjust their dietary intake of phenylalanine, with intake guided by blood phenylalanine concentration.	Sapropterin 10 mg/kg/day (could be increased to 20 mg/kg/day after 4 weeks if phenylalanine tolerance not increased by >20% compared with baseline) (n=27)  Phenylalanine-restricted diet only (n=29)	Change in phenylalanine tolerance <sup>1</sup> from baseline to week 26  Adverse events also reported (not primary outcome)
<b>Abbreviations:</b> ADHD, Attention deficit and hyperactivity disorder; PKU, phenylketonuria; RCT, randomised controlled trial			

Details of the excluded studies are listed in the section on [evidence selection](#).

## 4. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the [evidence summary table](#). The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

### Clinical effectiveness

This section considers whether sapropterin is clinically effective in people with PKU who need treatment to control phenylalanine levels, compared to no sapropterin treatment.

#### ***Blood phenylalanine concentration***

In a systematic review and meta-analysis of 4 RCTs by [Qu et al. \(2019\)](#) including 307 adults and children with PKU responsive to sapropterin, people treated with sapropterin for 3 to 6 weeks had statistically significantly lower blood phenylalanine concentrations compared with people treated with placebo or phenylalanine-restricted diet only (weighted mean difference [WMD] -100.37 micromol/litre, 95% confidence interval [CI]: -157.11 to -43.62, p=0.0005).

In a subgroup of people with lower concentrations of phenylalanine in their blood at baseline (less than 600 micromol/litre; 2 RCTs, n=101; study durations 4 weeks and 6 weeks), Qu et al. found there was no statistically significant difference between sapropterin and placebo or phenylalanine-restricted diet only over 4 to 6 weeks (WMD -7.75 micromol/litre, 95% CI -82.63 to 67.13, p=0.84). By contrast, in people with high blood phenylalanine levels at

baseline ( $\geq 600$  micromol/litre; 2 RCTs,  $n=206$ ; study durations 3 weeks and 6 weeks), sapropterin statistically significantly reduced blood phenylalanine concentration by about 200 micromol/litre over 3 to 6 weeks (WMD  $-225.31$  micromol/litre, 95% CI,  $-312.28$  to  $-138.34$ ,  $p<0.00001$ ) compared with placebo. 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.

The meta-analysis is limited by the short duration of the included studies. A prospective registry study by [Longo et al. \(2015\)](#) followed 504 adults and children who had taken sapropterin continuously for up to 7 years (median dose 20 mg/kg/day for a median of 4 years). After 5 years ( $n=48$ ), a statistically significant 199 micromol/litre improvement in mean blood phenylalanine concentrations was seen compared with baseline (392 micromol/litre compared with 591 micromol/litre,  $p=0.0009$ ). Similar results were seen at earlier yearly timepoints, and the numbers of participants in the analyses at those timepoints were higher (for example,  $n=333$  at 1 to 2 years; 415 micromol/litre compared with 591 micromol/litre,  $p=0.0001$ ).

This reviewer could not identify a published minimal clinically important difference for blood phenylalanine concentration. The SPC for sapropterin defines a satisfactory response to treatment as a reduction of 30% or more in blood phenylalanine concentration from baseline or attainment of target blood levels. In the RCTs included in Qu et al., participants were known to respond to sapropterin at baseline.

### ***Blood phenylalanine concentration in recommended range***

A double-blind RCT by [Levy et al. \(2007\)](#) involving 89 adults and children with PKU responsive to sapropterin treatment found a higher proportion of people were able to maintain their blood phenylalanine below 600 micromol/litre at 6 weeks when treated with sapropterin (22/41, 54%) compared with placebo (11/47, 23%). The statistical significance of this difference was not reported but the result suggests that, after 6 weeks, over half of people treated with sapropterin had phenylalanine levels within the recommended limits set out in the [European guidelines on the management of PKU](#).

### ***Stability of blood phenylalanine concentration***

A small observational study in 37 adults and children ([Burton et al. 2010](#)) found that blood phenylalanine concentrations varied less when people were treated with sapropterin compared with the pre-treatment period (mean within subject variance 4.799 compared with 6.897 respectively,  $p=0.0017$ , statistically significant). The result provided is a summary estimate of individual results presented in a graph. Information regarding estimated timepoints cannot be extrapolated from the graph. It is unclear, from this study, how this improvement affects patient-orientated outcomes such as cognitive function.

### ***Phenylalanine tolerance***

In the meta-analysis by Qu et al., 2 RCTs ( $n=99$ ) considered how much phenylalanine (from diet and supplements) a person with PKU could tolerate while keeping their blood phenylalanine levels within a predefined range (less than 360 micromol/litre).

The meta-analysis found that people taking sapropterin for 10 to 26 weeks could tolerate about 20 mg/kg more phenylalanine each day compared with people treated with placebo or a phenylalanine-restricted diet only (WMD 19.89 mg/kg/day, 95% CI 10.26 to 29.52,  $p < 0.0001$ ).

The prospective registry study by Longo et al. found that after 6 years ( $n=19$ ), mean dietary phenylalanine intake increased by about 200 mg/day (from  $1000 \pm 959$  mg/day to  $1197 \pm 667$  mg/day). Similar results were seen at earlier yearly timepoints and one later yearly timepoint ( $n=206$  at 1 year and  $n=5$  at 6 years). No statistical analyses were reported for this outcome.

These results suggest that sapropterin may enable people with PKU to have a less restrictive diet containing more natural protein.

### ***Protein and amino acid intake***

A small case-control study in 42 adults and children ([Evers et al. 2018](#)) looked at whether people who were taking sapropterin could increase their prescribed natural protein intake and reduce their prescribed amino acid 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 ( $p < 0.001$ ).

The amount of amino acid supplement people were advised to eat 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 are able to eat a less restrictive diet. Too few data were available to assess true natural protein intake; prescribed natural protein intake was assessed instead, which is easier to measure.

### **Safety and tolerability**

This section considers whether sapropterin is safe in people with PKU who require treatment to control phenylalanine levels, compared to no sapropterin treatment.

Four of the studies included in this evidence review considered the safety of sapropterin, including the meta-analysis of 4 trials (Qu et al. 2019) and 2 long-term studies giving data for up to 7 years (Burton et al. 2011 and Longo et al. 2015). Results of the study by Levy et al. are included in the meta-analysis by Qu et al.

Between 63% and 100% of participants in individual studies reported at least one adverse event. However, many of these were not considered to be related to study treatment (between 6% and 33% of adverse events were considered sapropterin-related in individual studies). The majority of adverse events were mild or moderate in severity, and adverse events leading to withdrawal from the studies were rare.

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. The meta-analysis by Qu et al. found no statistically significant differences between sapropterin and control for any adverse events assessed (abdominal pain, diarrhoea, pyrexia, cough, vomiting, upper respiratory tract infection, headache and oropharyngeal pain).

In the [European Public Assessment report \(EPAR\) for sapropterin](#) the regulators concluded that sapropterin was well tolerated. The EPAR states that hypophenylalaninaemia (defined as blood phenylalanine 26 micromol/litre or less) was more common in people treated with sapropterin compared with placebo, noting that this is an expected result with sapropterin lowering phenylalanine levels and may indicate a need to increase dietary phenylalanine or adjust the sapropterin dose.

The SPC for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in  $\geq 1/10$  people treated with sapropterin. Common adverse reactions (occurring in  $\geq 1/100$  to  $< 1/10$  people treated with sapropterin) listed in the SPC are hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

### **Cost effectiveness**

This section considers whether sapropterin is cost-effective in people with PKU who require treatment to control phenylalanine levels, compared to no sapropterin treatment.

No studies were identified during literature searches (see [search strategy](#) for full details) that compared the cost effectiveness of sapropterin with no sapropterin treatment in people with PKU. None of the studies included in this evidence review included an outcome investigating cost effectiveness.

### **Benefits of treatment by subgroup**

This section considers whether there is evidence for subgroups of people who demonstrate better outcomes with sapropterin therapy.

The most clearly defined subgroup of people who are more likely to benefit from sapropterin are those who are responsive to sapropterin. In the studies included in this evidence review, treatment with sapropterin was limited to people who had a positive response to a short, test course of sapropterin. The methods for determining response varied between studies, but in general, participants received a 2 to 4 week course of sapropterin and had their phenylalanine re-measured. Participants with a marked reduction in phenylalanine from baseline, normally 20-30%, were considered sapropterin responders and continued treatment with sapropterin.

Most studies included in this evidence review did not report efficacy and safety by subgroup.

Qu et al. looked at the change in blood phenylalanine concentration in subgroups of people with different blood phenylalanine concentrations at baseline. The results of these analyses suggest that people with blood phenylalanine concentrations of more than 600 micromol/litre of phenylalanine more likely to respond to sapropterin treatment over 6 weeks than people blood phenylalanine concentrations of less than 600 micromol/litre. 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.

The prospective registry study by Longo et al. reported that safety and efficacy data for children aged under 4 years (n=69) were similar to results in the overall population (n=1,189).

## 5. Discussion

### Evidence strengths and limitations

The studies included in this evidence review are of variable quality, ranging from a meta-analysis of high quality, double-blind RCTs to low quality, retrospective observational studies. The lower quality studies were included in the review because they reported on outcomes that were not included in the higher quality studies or provided evidence for outcomes over a longer duration.

The meta-analysis (Qu et al. 2018) included in the evidence review is affected by the limitations of the included RCTs.

The RCTs were all small, randomising fewer than 100 participants across all treatment arms, which is usual for rare conditions such as PKU because of the limited number of eligible participants. It is reassuring that many of the RCTs reported power calculations, and most would appear to have been adequately powered for their primary outcome. Three of the included studies (Levy et al. 2007, Trefz et al. 2009 and Muntau et al. 2017) had a high risk of reporting bias and all studies showed low risk of attrition bias. Muntau et al. had a high risk of selection, performance and detection bias. All of the included RCTs were sponsored by the pharmaceutical manufacturers and may be affected by publication bias. The older RCTs included in this review were of short duration (for example, Levy et al. 2007 lasted 6 weeks and Trefz et al. 2009 lasted 10 weeks), although open-label extension and registry studies provide longer-term efficacy and safety data.

It is difficult to assess the clinical relevance of some of the outcomes discussed in this evidence review because they do not have published minimal clinically important differences. Also, results for many of the outcomes should be interpreted with caution because they are disease-orientated outcomes, such as blood test results, which are not proven to result in benefits in patient-orientated outcomes, for example, cognitive functioning or physical growth.

Some of the disease-orientated outcomes reported in this evidence review, namely blood phenylalanine concentration and phenylalanine tolerance, are from meta-analyses and high quality RCTs. However, others, such as stability of blood phenylalanine concentration, and protein intake and amino acid intake, are only reported in lower quality observational studies, which have many limitations affecting their application to clinical practice.

No evidence was found to determine whether or not sapropterin is a cost-effective treatment option for adults or children with PKU.

## Other treatments

No other treatments are generally considered at the same stage in the treatment pathway for phenylketonuria as sapropterin.

## 6. Conclusion

The studies included in this evidence review suggest that sapropterin reduces blood phenylalanine concentrations and increases phenylalanine tolerance in adults and children with PKU compared with phenylalanine-restricted diet alone. These effects appear to be maintained with long-term treatment. Some limited evidence suggests blood phenylalanine concentrations were more stable when people were treated with sapropterin.

People treated with sapropterin in one study were able to increase the natural protein in their diet, and decrease the amount of amino acid supplement they took, although this is difficult to quantify because it is not known how well people adhered to the prescribed quantities and actual intake was not assessed.

More research is needed to show whether changes in phenylalanine blood concentrations and diet are reflected in benefits in patient-orientated outcomes (for example, cognitive functioning or physical growth).

All the studies assessed response to sapropterin treatment before starting the medicine, although the methods used to do this varied. In line with the marketing authorisation, only people with a positive response (when phenylalanine blood levels were monitored) were continued on sapropterin.

Adverse events were relatively common in people treated with sapropterin, although these were generally mild to moderate in severity, and did not require treatment to be stopped. Adverse events reported in studies included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia.

## 7. Evidence summary table

Use of sapropterin to treat phenylketonuria							
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
Study reference 1: <a href="#">Qu et al. 2019</a>							
S1- Meta-analysis of existing data analysis	<p>Systematic review and meta-analysis of 4 randomised controlled trials (RCTs): Levy et al. 2007, Trefz et al. 2009, Burton et al. 2015 and Muntau et al. 2017.</p> <p>307 people with PKU. Participants were stratified according to the severity of PKU at baseline.</p> <p>Baseline characteristics of the total study population were not reported. Details of the study by Levy et al. 2007 are shown below. Details of the studies by Trefz et al. 2009, Burton et al. 2015 and Muntau et al. 2017 are shown in <a href="#">Table 2</a>.</p>	<p>Sapropterin (n=162, dosage range 10–20 mg/kg/day)</p> <p>Placebo or no supplementation (n=145)</p> <p>Participants could be following phenylalanine-restricted diet or not</p>	Primary Clinical effectiveness	Change in blood phenylalanine concentration <sup>†</sup>	<p><b>Overall</b> (4 RCTs, n=307)</p> <p>Over 3–6 weeks, sapropterin statistically significantly reduced blood phenylalanine concentration compared with placebo (weighted mean difference [WMD] –100.37 micromol/litre, 95% confidence interval [CI]: –157.11 to –43.62, p=0.0005).</p> <p><b>Low baseline blood phenylalanine level</b> (&lt;600 micromol/litre; 2 RCTs, n=101)</p> <p>Over 4–6 weeks, there was no statistically significant difference between sapropterin and placebo (WMD –7.75 micromol/litre, 95% CI –82.63 to 67.13, p=0.84).</p> <p><b>High baseline blood phenylalanine level</b> (≥600 micromol/litre; 2 RCTs, n=206)</p>	8/10	Direct study focusing on people with the indication and characteristics of interest

					Over 3–6 weeks, sapropterin statistically significantly reduced blood phenylalanine concentration compared with placebo (WMD -225.31 micromol/litre, 95% CI -312.28 to -138.34, p<0.00001).		
			Secondary Clinical effectiveness	Change in phenylalanine tolerance <sup>1</sup>	In 2 RCTs (n=99) over 10–22 weeks, sapropterin statistically significantly improved dietary phenylalanine tolerance compared with placebo (WMD 19.89 mg/kg/day, 95% CI 10.26 to 29.52, p<0.0001).		
			Secondary Safety	Adverse events  Data was combined for common adverse events in the 4 RCTs including abdominal pain, diarrhoea, pyrexia, cough, vomiting, upper respiratory tract infection, headache and oropharyngeal pain.	There were no statistically significant differences between sapropterin and placebo for any adverse events assessed.		
<p><b>Critical appraisal summary:</b> The study is limited by the small sample sizes and short durations of the included RCTs and a focus on disease-orientated efficacy outcomes. Three of the included studies (Levy et al. 2007, Trefz et al. 2009 and Muntau et al. 2017) had a high risk of reporting bias and all studies showed low risk of attrition bias. Muntau et al. 2017 had a high risk of selection, performance and detection bias. All the included RCTs were sponsored by the pharmaceutical manufacturers and may be affected by publication bias.</p>							

<sup>1</sup> There is no published minimal clinically important difference for this outcome, see the [Results section](#) for a discussion on the clinical relevance of these results.

**Study reference 2:** [Levy et al. 2007](#)

P1- Double-blind, randomised control trial	<p>16 centres in North America and 14 centres in Europe.</p> <p>89 adults and children aged ≥8 years (mean age 20.4 years, 58% male) with phenylketonuria responsive to sapropterin treatment (defined as a reduction of 30% or more in blood phenylalanine concentration after sapropterin 10 mg/kg for 8 days).</p> <p>Participants were required to have blood phenylalanine ≥600 micromol/ litre (450 micromol/ litre after protocol amendment).</p>	<p>Sapropterin 10 mg/kg daily (n=42)</p> <p>Placebo (n=47)</p> <p>Participants were not following a phenylalanine-restricted diet at baseline and were required to continue their diet unchanged throughout the study period.</p>	Primary Clinical effectiveness	<p>Change in blood phenylalanine concentration<sup>1</sup> from baseline to week 6.</p> <p>(included in meta-analysis)</p>	<p>The mean change in the sapropterin group was -235.9 micromol/litre (from 842.7 micromol/litre at baseline).</p> <p>The mean change in the placebo group was +2.9 micromol/litre (from 888.3 micromol/litre at baseline).</p> <p>Statistically significant difference between groups of -245 micromol/litre (SD 52.5), p=0.0002.</p>	7/10	Direct study focusing on people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	<p>Proportion of patients with blood phenylalanine concentration below 600 micromol/ litre at week 6.</p>	<p>In the sapropterin group, 17% (7/41) had blood phenylalanine levels &lt;600 micromol/litre at screening. This increased to 54% (22/41) by week 6.</p> <p>In the control group, 19% (9/47) had blood phenylalanine levels &lt;600 micromol/litre at screening. This increased to 23% (11/47) by week 6.</p>		

			Secondary Safety	Adverse events	<p>Across the whole study population, 55/88 participants (63%) reported a total of 148 adverse events.</p> <p>Adverse events possibly related to drug-treatment were reported by 20% (8/41) of people in the sapropterin group and 23% (11/47) of people in the placebo group. There was no statistically significant difference between groups (p=0.8).</p> <p>No participants withdrew from the study due to adverse events.</p> <p>The most common adverse events in the sapropterin group were upper respiratory tract infection (17%), headache (10%), vomiting (5%), diarrhoea (5%) and pyrexia (5%).</p>		
<p><b>Critical appraisal summary:</b> This is multicentre, double-blind, randomised controlled trial with a low risk of bias. Randomisation methods are reported by the authors and it would appear that allocation was concealed. All participants are accounted for, and intention-to-treat analysis was carried out. A power calculation is reported and the study would appear to be adequately powered. Baseline characteristics were generally comparable across treatment arms.</p> <p>The study is limited by a short, 6 week duration and a focus on disease-orientated efficacy outcomes.</p> <p><sup>1</sup> There is no published minimal clinically important difference for this outcome, see the <a href="#">Results section</a> for a discussion on the clinical relevance of these results.</p>							
<p><b>Study reference 3:</b> <a href="#">Burton et al. 2011</a></p>							
P1- Open-label extension study to Lee et al. 2008 and Trefz et al. 2009	15 centres in the United States, Canada and Europe (including sites in the UK)  111 people with PKU responsive to sapropterin who had completed Lee et al. 2008 and Trefz et	Sapropterin 5 mg to 20 mg/kg/day adjusted to control blood phenylalanine concentrations according to local clinical site recommendations (n=111)	Primary Safety	Adverse events up to 3 years	Adverse events were reported by 93/111 participants (83.8%), with 37/111 participants (33.3%) reporting drug-related adverse	7/10	Direct study focusing on people with the indication and

	<p>al. 2009, or withdrew from Trefz et al. 2009 due to elevated blood phenylalanine concentrations.</p> <p>Mean age was 16.4 years (range 4 to 50) and 60.4% were male.</p>	<p>No control</p> <p>The mean duration of treatment was 658.7 days (range 56 to 953 days).</p> <p>The study had no dietary restrictions and phenylalanine intake was not monitored. During the study by Lee et al, participants were not following a restricted diet, whereas in Trefz et al. participants followed a phenylalanine-restricted diet.</p>			<p>events. The most common drug-related adverse events were viral gastroenteritis, vomiting, and headache (each occurring in 4.5% of participants).</p> <p>21/111 participants (18.9%) withdrew from the study early.</p> <p>3 participants withdrew because of drug-related adverse events (difficulty concentrating, clinically significant decreased platelet count, and intermittent diarrhoea).</p>		<p>characteristics of interest.</p>
<p><b>Critical appraisal summary:</b> This is an open-label, extension study to a double-blind RCT. The open-label design means the study is susceptible to bias. Participants were required to have completed the run-in RCTs. All participants are accounted for.</p> <p>The lack of a control arm prevents conclusions on the relative safety of sapropterin.</p>							
<p><b>Study reference 4:</b> <a href="#">Longo et al. 2015</a></p>							
<p>P1- Prospective observational study (the PKUDOS registry)</p> <p>Interim analysis</p>	<p>52 sites in the United States</p> <p>1,189 people with PKU who had previously taken, were currently taking or intended to take sapropterin within 90 days of enrolment.</p> <p>The mean age was not reported but age ranged from 0 to 63 years. 8% of participants were aged &lt;4 years and 52% were female.</p> <p>The analysis focused on 2 populations: the uninterrupted use population (participants who had been taking sapropterin continuously) and the short-term use population (participants who were on sapropterin for up to 3 months only).</p> <p>Peak blood phenylalanine was <math>\geq 1200</math> micromol/litre in statistically significantly fewer people in the uninterrupted use population compared with the short-term use population</p>	<p>504 participants were continuously exposed to sapropterin following enrolment (uninterrupted use: median dose 20 mg/kg/day for a median of 4 years).</p> <p>211 participants stopped sapropterin within 3 months (short-term use: median dose 20 mg/kg/day for between 0.03 and 3 months).</p> <p>Exposure to sapropterin varied among the other 474 participants and these are not discussed.</p> <p>The study did not specify any dietary restrictions.</p>	<p>Primary</p> <p>Clinical effectiveness</p>	<p>Change in blood phenylalanine concentration<sup>1</sup> from baseline to over 5 years (&gt;5 years and <math>\leq 6</math> years)</p>	<p><b>Uninterrupted use population (n=48)</b></p> <p>A statistically significant 199 micromol/litre improvement in mean blood phenylalanine was seen (392 <math>\pm</math> 239 micromol/litre compared with 591 <math>\pm</math> 382 micromol/litre, <math>p=0.0009</math>).</p> <p><b>Short-term use population (n=30)</b></p> <p>A small improvement in mean blood phenylalanine was</p>	<p>6/10</p>	<p>Direct study focusing on people with the indication and characteristics of interest</p>

	<p>(43%, compared with 82%, p=0.0001), and more people were sapropterin-responsive (71% compared with 27% respectively, p=0.001).</p>				<p>seen but was not statistically significant (759 ±366 micromol/litre compared with 830 ±476 micromol/litre).</p> <p>Similar results were seen at earlier yearly timepoints, and the numbers of participants in the analyses at those timepoints were higher.</p> <p>For example, at 1 to 2 years, n=333 in the uninterrupted use population (415 micromol/litre compared with 591 micromol/litre, p=0.0001) and n=129 in the short-term use population (752 micromol/litre compared with 830 micromol/litre, no statistically significant difference).</p>		
			<p>Secondary Clinical effectiveness</p>	<p>Change in phenylalanine tolerance<sup>1</sup> from baseline to 6 years (5 years and ≤6 Years)</p>	<p><b>Uninterrupted use population (n=19):</b></p> <p>Mean dietary phenylalanine intake increased by 197 mg/day (from 1000 ±959 mg/day to 1197 ±667 mg/day).</p> <p>No statistical analyses were reported for this outcome.</p> <p>Similar results were seen at earlier yearly timepoints and one later yearly timepoint</p>		

					<p>(n=206 at 1 year and n=5 at 6 years).</p> <p><b>Short-term use population</b></p> <p>Mean dietary phenylalanine intake decreased at all timepoints.</p>		
			Secondary Safety	Adverse events	<p>6% (74/1189) of people had at least 1 adverse event considered sapropterin-related. These occurred most commonly (<math>\geq 1\%</math>) in the gastrointestinal, respiratory and nervous systems.</p> <p>There were 113 sapropterin-related adverse events. Of these, 73% were considered mild, 23% moderate, and 4% severe. Adverse events led to permanent discontinuation of sapropterin in 12% of people, temporary discontinuation in 10% of people and dose reductions in 4% of people.</p> <p>No deaths were reported.</p>		
<p><b>Critical appraisal summary:</b> This is a prospective, observational study, which is susceptible to bias, confounding and other methodological problems. Reporting to the PKUDOS registry is voluntary and data may be incomplete and is not verified. 52 centres were involved and there are likely to be differences in how they manage people with PKU. Originally the registry did not require baseline pre-sapropterin blood phenylalanine concentrations; therefore, not all participants have these data. Outcome assessment was not blinded, and there was no control group and outcomes are limited to comparisons of baseline to study end (7 years).</p>							
<p>Reference study 5: <a href="#">Burton et al. 2010</a></p>							

P1- Retrospective observational study	One US centre.37 adults and children (mean age 12.6 years, 57% female) with PKU responsive to sapropterin.	Sapropterin (mean dose 20 mg/kg/day) for at least 1 year (mean 19 months).  Compared outcomes in the periods before and after treatment initiation.  Most participants were on a phenylalanine-restricted diet.	Primary Clinical effectiveness	Stability of blood phenylalanine levels	A statistically significant improvement in variability of blood phenylalanine levels was seen with sapropterin compared with pre-treatment (mean [SD] within subject variance 4.799 [2.19] compared with 6.897 [2.62] respectively, p=0.0017).  The result provided is a summary estimate of individual results presented in a graph. Information regarding estimate timepoints cannot be extrapolated from the graph.	5/10	Direct study focusing on people with the indication and characteristics of interest.
<p><b>Critical appraisal summary:</b> This is a retrospective, observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessments were not blinded. Outcomes were compared before and after treatment and it is unclear how the population may have changed over time, apart from increasing age, which the authors note may cause underestimation of the impact of sapropterin on variability of phenylalanine because increasing age was associated with increasing variability.</p> <p>Although the study is of low quality, the authors report detailed results for the outcome of interest, including statistical analyses.</p>							
<p><b>Reference study 6:</b> <a href="#">Evers et al. 2018</a></p>							
P1- Retrospective case-control study	2 centres in The Netherlands. 42 people (mean age 13 years, 67% female) with PKU responsive to sapropterin.	21 people had been taking sapropterin (dose not reported) for at least 5.5 years.  These cases were matched (by age and gender) with 21 controls who did not take sapropterin  The study did not specify any dietary restrictions but all participants were regularly seen by a dietician.  Dietary assessments and recommendations for protein and amino acid supplement intake were done by different dieticians using	Clinical effectiveness	Change in prescribed natural protein intake over 5 years	A statistically significant increase in prescribed natural protein intake was seen in the sapropterin group compared with baseline (mean 0.66 ±0.26 g/kg/day compared with 0.43 ±0.28 g/kg/day respectively, p<0.001)  Natural protein intake was statistically significantly higher in the sapropterin group	5/10	Direct study focusing on people with the indication and characteristics of interest.

		<p>the same national dietary guidelines.</p> <p>Some people had a high prescribed natural protein intake at baseline; therefore, 2 people in the control group and 1 person in the treatment group were not prescribed amino acid supplements.</p> <p>No differences in blood phenylalanine concentrations were seen between the groups.</p>			<p>than in the control group (0.66 <math>\pm</math>0.26 g/kg/day compared with 0.38 <math>\pm</math>0.31 g/kg/day respectively, p&lt;0.001).</p>		
			Clinical effectiveness	Change in prescribed amino acid supplement intake over 5 years	<p>A statistically significant decrease in prescribed amino acid supplement intake was seen in the sapropterin group compared with baseline (mean 0.32 <math>\pm</math>0.34 g/kg/day compared with 0.99 <math>\pm</math>0.51 g/kg/day respectively, p&lt;0.001).</p> <p>Amino acid supplement intake was statistically significantly lower in the sapropterin group than in the control group (0.32 <math>\pm</math>0.34 g/kg/day compared with 0.74 <math>\pm</math>0.45 g/kg/day, p=0.002).</p>		
<p><b>Critical appraisal summary:</b> This is a retrospective, observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessments were not blinded. Prescribed natural protein intake was assessed because too few data were available to assess true natural protein intake. It is unknown how well people adhered to the prescribed protein and amino acid supplement intakes.</p> <p>Although the study is of low quality, the authors report detailed results for the outcome of interest, including statistical analyses.</p>							

## 8. Grade of evidence table

Use of sapropterin compared with diet only (with or without placebo) to treat phenylketonuria (PKU)					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Blood phenylalanine concentration	Qu et al. 2019	8/10	Direct study	A	<p>This outcome looked at how much phenylalanine is in a person's blood. Raised phenylalanine levels are thought to result in neurotoxicity.</p> <p>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).</p> <p>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). However, 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&lt;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.</p> <p>These studies suggest that sapropterin reduces phenylalanine blood concentration (statistically significant), particularly in people with high phenylalanine in their blood before treatment.</p> <p>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.</p>
	Longo et al. 2015	6/10	Direct study		
Phenylalanine tolerance	Qu et al. 2019	8/10	Direct study	A	<p>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 (&lt;360 micromol/litre).</p> <p>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&lt;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.</p> <p>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.</p>
	Longo et al. 2015	6/10	Direct study		

**Use of sapropterin compared with diet only (with or without placebo) to treat phenylketonuria (PKU)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					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.
Blood phenylalanine concentration below 600 micromol/litre	Levy et al. 2007	7/10	Direct study	B	<p>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.</p> <p>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).</p> <p>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.</p>
Stability of blood phenylalanine concentrations	Burton et al. 2010	5/10	Direct study	C	<p>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.</p> <p>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, <math>p=0.0017</math>, statistically significant).</p> <p>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.</p>
Natural protein intake	Evers et al. 2018	5/10	Direct study	C	<p>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.</p> <p>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 (<math>p&lt;0.001</math>, statistically significant). At 5 years, natural protein intake was 280 mg/kg/day higher in the sapropterin group than in the control group (<math>p&lt;0.001</math>, statistically significant).</p> <p>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,</p>

**Use of sapropterin compared with diet only (with or without placebo) to treat phenylketonuria (PKU)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					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.
Amino acid supplement intake	Evers et al. 2018	5/10	Direct study	C	<p>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.</p> <p>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 (<math>p &lt; 0.001</math>, statistically significant). At 5 years, amino acid intake was 420 mg/kg/day lower in the sapropterin group than in the control group (<math>p = 0.002</math>, statistically significant).</p> <p>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</p>
Adverse events	Qu et al. 2019	8/10	Direct study	A	<p>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.</p> <p>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 study the 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.</p> <p>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.</p> <p>These results suggest that sapropterin is well tolerated.</p>
	Burton et al. 2011	7/10	Direct study		
	Longo et al. 2015	6/10	Direct study		

## 9. Literature search terms

Search strategy	
<p><b>P – Patients / Population</b></p> <p>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	<p>Individuals with PKU of all ages who require treatment to maintain phenylalanine levels in therapeutic range.</p> <p>Subgroups including but not limited to:</p> <ul style="list-style-type: none"> <li>• Children and young people up to 25</li> <li>• Individuals with comorbidities that negatively impact on dietary adherence</li> <li>• Individuals with neuropsychiatric impairments</li> <li>• Individuals whose primary caregivers have specific issues that negatively impact on delivering the PKU diet.</li> </ul>
<p><b>I – Intervention</b></p> <p>Which intervention, treatment or approach should be used?</p>	<p>Sapropterin in combination with current standard treatment of phenylalanine-restricted diet with artificial amino acid, vitamin and mineral supplement.</p>
<p><b>C – Comparison</b></p> <p>What is/are the main alternative/s to compare with the intervention being considered?</p>	<p>No sapropterin and current standard treatment of phenylalanine-restricted diet with artificial amino acid, vitamin and mineral supplement alone.</p>
<p><b>O – Outcomes</b></p> <p>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission</p>	<p><u>Critical to decision-making:</u></p> <ul style="list-style-type: none"> <li>• Blood phenylalanine concentrations</li> </ul> <p><u>Important to decision-making:</u></p> <ul style="list-style-type: none"> <li>• Blood phenylalanine variability</li> <li>• Quantity of artificial amino acid supplement required for nutritional health</li> <li>• Proportion of patients attaining phenylalanine levels within treatment range</li> <li>• Amount of natural protein in diet (within standard phenylalanine ranges)</li> <li>• Safety outcomes</li> <li>• Cost effectiveness outcomes</li> </ul>
Assumptions / limits applied to search	

*Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.*

- Study designs: Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.
- Non-English language studies will be excluded.
- Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials will not be included. Papers published longer than 20 years ago will be excluded.

## 10. Search strategy

### Database search strategies

#### Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) <1946 to December 04, 2019>

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: 396

Search strategy:

Database: Ovid MEDLINE(R) <1946 to December 04, 2019>

Search Strategy:

- 
- 1 sapropterin.ti,ab. (99)
  - 2 tetrahydrobiopterin.ti,ab. (3126)
  - 3 bh4.ti,ab. (1613)
  - 4 thb.ti,ab. (650)
  - 5 kuan.ti,ab. (21)
  - 6 phenoptin.ti,ab. (2)
  - 7 or/1-6 (4241)
  - 8 Phenylketonuria\*.ti,ab. (5323)
  - 9 PKU.ti,ab. (2521)
  - 10 "folling\* disease".ti,ab. (32)
  - 11 ((pah or "phenylalanine hydroxylase") adj2 deficien\*).ti,ab. (337)
  - 12 "oligophrenia phenylpyruvica".ti,ab. (9)
  - 13 hyperphenylalaninaemia.ti,ab. (318)
  - 14 exp Phenylketonurias/ (6970)
  - 15 or/8-14 (7933)
  - 16 7 and 15 (604)
  - 17 limit 16 to english language (555)
  - 18 limit 17 to yr="1999 -Current" (420)
  - 19 animals/ not humans/ (4617942)
  - 20 18 not 19 (396)

#### Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 13, 2019>

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: 49

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to December 13, 2019>

Search Strategy:

- 
- 1 sapropterin.ti,ab. (28)
  - 2 tetrahydrobiopterin.ti,ab. (153)
  - 3 bh4.ti,ab. (399)
  - 4 thb.ti,ab. (94)
  - 5 kuan.ti,ab. (7)
  - 6 phenoptin.ti,ab. (0)
  - 7 or/1-6 (574)
  - 8 Phenylketonuria\*.ti,ab. (343)

- 9 PKU.ti,ab. (275)
- 10 "folling\* disease".ti,ab. (1)
- 11 ((pah or "phenylalanine hydroxylase") adj2 deficien\*).ti,ab. (20)
- 12 "oligophrenia phenylpyruvica".ti,ab. (0)
- 13 hyperphenylalaninaemia.ti,ab. (5)
- 14 exp Phenylketonurias/ (0)
- 15 or/8-14 (396)
- 16 7 and 15 (49)
- 17 limit 16 to english language (49)
- 18 limit 17 to yr="1999 -Current" (49)
- 19 animals/ not humans/ (0)
- 20 18 not 19 (49)

**Database: Medline epubs ahead of print**

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <December 13, 2019>

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: 10

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <December 13, 2019>

Search Strategy:

- 
- 1 sapropterin.ti,ab. (7)
  - 2 tetrahydrobiopterin.ti,ab. (22)
  - 3 bh4.ti,ab. (26)
  - 4 thb.ti,ab. (11)
  - 5 kuan.ti,ab. (4)
  - 6 phenoptin.ti,ab. (1)
  - 7 or/1-6 (48)
  - 8 Phenylketonuria\*.ti,ab. (39)
  - 9 PKU.ti,ab. (31)
  - 10 "folling\* disease".ti,ab. (0)
  - 11 ((pah or "phenylalanine hydroxylase") adj2 deficien\*).ti,ab. (4)
  - 12 "oligophrenia phenylpyruvica".ti,ab. (0)
  - 13 hyperphenylalaninaemia.ti,ab. (0)
  - 14 exp Phenylketonurias/ (0)
  - 15 or/8-14 (44)
  - 16 7 and 15 (11)
  - 17 limit 16 to english language (11)
  - 18 limit 17 to yr="1999 -Current" (10)
  - 19 animals/ not humans/ (0)
  - 20 18 not 19 (10)

**Database: Medline daily update**

Platform: Ovid

Version:

Search date:

Number of results retrieved:

Search strategy

**Database: Embase**

Platform: Ovid

Version: Embase <1974 to 2019 Week 50>

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: 468

Search strategy:

Database: Embase <1974 to 2019 Week 50>

Search Strategy:

- 
- 1 sapropterin/ (578)
  - 2 sapropterin.ti,ab. (304)
  - 3 tetrahydrobiopterin.ti,ab. (4330)
  - 4 bh4.ti,ab. (3262)
  - 5 thb.ti,ab. (1046)
  - 6 kuan.ti,ab. (107)
  - 7 phenoptin.ti,ab. (2)
  - 8 or/1-7 (6668)
  - 9 Phenylketonuria\*.ti,ab. (6358)
  - 10 PKU.ti,ab. (4198)
  - 11 "folling\* disease".ti,ab. (11)
  - 12 ((pah or "phenylalanine hydroxylase") adj2 deficien\*).ti,ab. (516)
  - 13 "oligophrenia phenylpyruvica".ti,ab. (0)
  - 14 hyperphenylalaninaemia.ti,ab. (310)
  - 15 phenylketonuria/ (8177)
  - 16 or/9-15 (9295)
  - 17 8 and 16 (1070)
  - 18 limit 17 to english language (1000)
  - 19 limit 18 to yr="1999 -Current" (878)
  - 20 19 not (letter or editorial).pt. (861)
  - 21 20 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (495)
  - 22 nonhuman/ not human/ (4512061)
  - 23 21 not 22 (468)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL**

Platform: Wiley

Version:

CDSR –Issue 12 of 12, Dec 2019

CENTRAL – Issue 12 of 12, Dec 2019

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: CDSR – 1 ; CENTRAL – 26.

- #1 (sapropterin):ti,ab,kw 59
- #2 (tetrahydrobiopterin):ti,ab,kw 128
- #3 (bh4):ti,ab,kw 96
- #4 (thb):ti,ab,kw 84
- #5 (kuan):ti,ab,kw 24
- #6 (phenoptin):ti,ab,kw 3
- #7 #1 or #2 or #3 or #4 or #5 or #6 261
- #8 (Phenylketonuria\*):ti,ab,kw 304
- #9 (PKU):ti,ab,kw 234
- #10 "folling\* disease":ti,ab,kw 0
- #11 ((pah or "phenylalanine hydroxylase") near/2 deficien\*):ti,ab,kw 14
- #12 ("oligophrenia phenylpyruvica"):ti,ab,kw 0
- #13 (hyperphenylalaninaemia):ti,ab,kw 12
- #14 MeSH descriptor: [Phenylketonurias] explode all trees 125
- #15 #8 or #9 or #10 or #11 or #12 or #13 or #14 358

#16 #7 and #15 56  
 #17 "conference":pt or "clinicaltrials.gov":so or "www.who.int":so 444345  
 #18 #16 not #17 27

**Database: HTA and DARE**

Platform: CRD

Version: Up to 2018

Search date: 16<sup>th</sup> Dec 2019

Number of results retrieved: HTA – 2, DARE – 2

Search strategy:

1	(sapropterin)	3	Delete		
2	(tetrahydrobiopterin)	2	Delete		
3	(bh4)	2	Delete		
4	(thb)	27	Delete		
5	(kuvan)	0	Delete		
6	(phenoptin)	0	Delete		
7	(#1 or #2 or #3 or #4 or #5 or #6)	32	Delete		
8	(Phenylketonuria*)	35	Delete		
9	(PKU)	19	Delete		
10	("folling* disease")	0	Delete		
11	((("pah or "phenylalanine hydroxylase") near2 deficien*))	2	Delete		
12	("oligophrenia phenylpyruvica")	0	Delete		
13	(hyperphenylalaninaemia)	1	Delete		
14	MeSH DESCRIPTOR Phenylketonurias EXPLODE ALL TREES	17			
	Delete				
15	(#8 or #9 or #10 or #11 or #12 or #13 or #14)	39	Delete		
16	(#7 and #15)	4	Delete		

**Trials registry search strategies**

***Clinicaltrials.gov***

Search date: 12<sup>th</sup> Dec 2019

Number of results retrieved: 12

Search strategy: Sapropterin AND Phenylketonuria (limited to phase 3 & 4 trials)

***Clinicaltrialsregister.eu***

Search date: 12<sup>th</sup> Dec 2019

Number of results retrieved: 12

Search strategy: Sapropterin AND Phenylketonuria (limited to phase 3 & 4 trials)

**11. Evidence selection**

A literature search was conducted which identified 572 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and 19 references were obtained and assessed for relevance. Of these, 9 references are included in the evidence summary. The remaining 10 references were excluded and are listed in the following table.

Study reference	Reason for exclusion
Aldamiz-Echevarria, Luis, Bueno, Maria A, Couce, Maria L et al. (2015) 6R-tetrahydrobiopterin treated PKU patients below 4 years of age: Physical outcomes, nutrition and genotype. <i>Molecular genetics and metabolism</i> 115(1): 10-6	Study not prioritised (not the best available evidence) Data on PICO outcomes reported in higher quality studies
Feldmann, Reinhold, Wolfgart, Eva, Weglage, Josef et al. (2017) Sapropterin treatment does not enhance the health-related quality of life of patients with phenylketonuria and their parents. <i>Acta paediatrica (Oslo, Norway: 1992)</i> 106(6): 953-959	Study not prioritised (not the best available evidence) Data on PICO outcomes reported in higher quality studies
Keil S, Anjema K, van Spronsen et al. (2013) Long-term follow-up and outcome of phenylketonuria patients on sapropterin: a retrospective study. <i>Pediatrics</i> 131(6), e1881–8	Study not prioritised (not the best available evidence) Data on PICO outcomes reported in higher quality studies
Lee, Phillip, Treacy, Eileen P, Crombez, Eric et al. (2008) Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. <i>American journal of medical genetics. Part A</i> 146a (22): 2851-9	Study not prioritised (not the best available evidence) Data on long-term outcomes reported in higher quality studies
Lindgren M, Krishnaswami S, Reimschisel T et al. (2013) A Systematic Review of BH4 (Sapropterin) for the Adjuvant Treatment of Phenylketonuria. <i>JIMD reports</i> 8, 109–19	Systematic review of only 2 studies – systematic review of 4 studies included
Longo, Nicola, Siriwardena, Komudi, Feigenbaum, Annette et al. (2015) Long-term developmental progression in infants and young children taking sapropterin for phenylketonuria: a two-year analysis of safety and efficacy. <i>Genetics in medicine: official journal of the American College of Medical Genetics</i> 17(5): 365-73	Study not prioritised (not the best available evidence) Data on PICO outcomes reported in higher quality studies
Shintaku H and Ohura T (2014) Sapropterin is safe and effective in patients less than 4-years-old with BH4-responsive phenylalanine hydrolase deficiency. <i>The Journal of pediatrics</i> 165(6), 1241–4	Study not prioritised (not the best available evidence) Data on PICO outcomes reported in higher quality studies
Somaraju UR and Merrin M (2015) Sapropterin dihydrochloride for phenylketonuria. <i>Cochrane Database of Systematic Reviews</i> (3)	Systematic review of only 2 studies – systematic review of 4 studies included
Trefz FK, Muntau AC, Lagler FB et al. (2015) The Kuvan Adult Maternal Paediatric European Registry (KAMPER) Multinational Observational Study: Baseline and 1-Year Data in Phenylketonuria Patients Responsive to Sapropterin. <i>JIMD reports</i> 23, 35–43	Study not prioritised (not the best available evidence) Data on long-term safety reported in higher quality studies
Zori, R., Ahring, K., Burton, B., et al (2019). Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria. <i>Molecular Genetics and Metabolism</i> 128(12); 92-101	Study not prioritised (not the best available evidence) Sapropterin (plus diet) is the comparator only. Data on PICO outcomes reported in higher quality studies

## 12. Related NICE guidance and NHS England clinical policies

NHS England has published Clinical Commissioning Policies on:

[The use of Sapropterin in children with Phenylketonuria \(2015\)](#)

[Sapropterin for Phenylketonuria: Use in Pregnancy \(2013\)](#)

A NICE Technology Appraisal has been proposed for:

[Sapropterin for treating phenylketonuria \(ID1475\)](#)

## 13. Terms used in this evidence summary

### Abbreviations

Term	Definition
ADHD	Attention deficit and hyperactivity disorder
BH4	Tetrahydrobiopterin
EPAR	European Public Assessment Report
PKU	Phenylketonuria
RCT	Randomised controlled trial
SPC	Summary of Product Characteristics

### Medical definitions

Term	Definition
Amino acid	Building blocks of protein
Hyperphenylalaninaemia	Raised phenylalanine concentration in the blood and body fluids
Phenylalanine	An essential amino acid provided by protein in the diet
Phenylalanine hydroxylase	Enzyme responsible for the conversion of phenylalanine
Phenylketonuria	An autosomal recessive genetic disorder characterised by an increase of phenylalanine in the blood and body fluids

## 14. References

Browna CS and Lichter-Koneckib U (2015) [Phenylketonuria \(PKU\): A problem solved?](#) Molecular Genetics and Metabolism Reports 6: 8–12

Burton BK, Bausell H, Katz R et al. (2010) [Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria \(PKU\)](#). Molecular Genetics and Metabolism 101(2-3), 110–4

Burton BK, Nowacka M, Hennermann JB et al. (2011) [Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: results of a phase 3b study](#). Molecular Genetics and Metabolism 103(4), 315–22

- Burton B, Grant M, Feigenbaum A et al. (2015) [A randomized, placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria](#). *Molecular Genetics and Metabolism* 114(3), 415–24
- Enns GM, Koch R, Brumm V et al. (2010) [Suboptimal outcomes in patients with PKU treated early with diet alone: Revisiting the evidence](#). *Molecular Genetics and Metabolism* 101(2-3), 99–109
- Evers RAF, van Wegberg AMJ, van Dam E et al. (2018) [Anthropomorphic measurements and nutritional biomarkers after 5years of BH4 treatment in phenylketonuria patients](#). *Molecular Genetics and Metabolism* 124(4): 238–242
- Jurecki ER, Cederbaum S, Kopesky J et al. (2017) [Adherence to clinic recommendations among patients with phenylketonuria in the United States](#). *Molecular Genetics and Metabolism* 120(3), 190–7
- Lee P, Treacy EP, Crombez E et al. (2008) [Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria](#). *American Journal of Medical Genetics*. 146A (22), 2851–9
- Levy HL, Milanowski A, Chakrapani A et al. (2007) [Efficacy of sapropterin dihydrochloride \(tetrahydrobiopterin, 6R-BH4\) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study](#). *The Lancet* 370(9586), 504–10
- Longo N, Arnold GL, Pridjian G et al. (2015) [Long-term safety and efficacy of sapropterin: the PKUDOS registry experience](#). *Molecular genetics and metabolism* 114(4), 557–63
- Muntau AC, Burlina A, Eyskens F et al. (2017) [Efficacy, safety and population pharmacokinetics of sapropterin in PKU patients <4 years: results from the SPARK open-label, multicentre, randomized phase IIIb trial](#). *Orphanet Journal of Rare Diseases* 12(1), 47
- Qu J, Yang T, Wang E et al. (2019) [Efficacy and safety of sapropterin dihydrochloride in patients with phenylketonuria: A meta-analysis of randomized controlled trials](#). *British Journal of Clinical Pharmacology* 85(5): 893–9
- Somaraju UR and Merrin M. [Sapropterin dihydrochloride for phenylketonuria](#). *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD008005. DOI: 10.1002/14651858.CD008005.pub4
- Trefz FK, Burton BK, Longo N et al. (2009) [Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study](#). *The Journal of Pediatrics* 154(5), 700–7

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