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Advising on new medicines for Scotland
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NHS SCOTLAND
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sapropterin dihydrochloride, 100mg, soluble tablets (Kuvan®) SMC No 558/09

BioMarin Europe Limited

6 July 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

sapropterin dihydrochloride (Kuvan®) is not recommended for use within NHS Scotland.

Indication under review: the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment.

In phase III studies in patients with a diagnosis of PKU, sapropterin was associated with a statistically significant reduction in blood phenylalanine concentration over placebo in one study, and statistically significant increases in phenylalanine tolerance when added to a phenylalanine-restricted diet compared with a phenylalanine-restricted diet alone in two other studies, one of which was placebo controlled.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Published 13 August 2018

Indication

Sapropterin dihydrochloride is indicated for the treatment of hyperphenylalaninaemia in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment.[1]

Dosing Information

The starting dose of sapropterin in adult and paediatric patients with PKU is 10mg/kg body weight once daily. Tablets should be dissolved in water and taken with a meal at the same time each day, preferably in the morning. The dose is adjusted, usually between 5 and 20mg/kg/day, to achieve and maintain adequate blood phenylalanine levels as defined by the physician.[1, 2]

Before patients are maintained on sapropterin they should undergo a one month test period to evaluate the response to sapropterin. A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within a one month test period should be considered non-responsive, these patients should not be treated with sapropterin and administration of sapropterin should be discontinued.[1]

For information on dose adjustments and administration see the summary of product characteristics (SPC).[1]

Treatment with sapropterin must be initiated and supervised by a physician experienced in the treatment of PKU.[1]

Product availability date

December 2008

Sapropterin has been designated as an orphan medicine by the European Medicines Agency and meets SMC orphan criteria

Summary of evidence on comparative efficacy

Sapropterin is a synthetic form of tetrahydrobiopterin (BH4), a naturally occurring co-factor for phenylalanine hydroxylase. PKU is a recessive genetic condition, producing a deficiency in functioning phenylalanine hydroxylase, with a reduction or loss of ability to metabolise phenylalanine. In patients with BH4 responsive PKU, sapropterin may enhance the residual enzyme activity of phenylalanine hydroxylase, thereby reducing blood phenylalanine levels.[1]

Following the initial submission, the company requested that SMC considered sapropterin when positioned for use in the paediatric PKU population i.e. 0 to 18 year olds, uncontrolled (elevated phenylalanine with symptoms) and partially controlled (phenylalanine within target levels with presence of symptoms), who have been shown to be responsive to sapropterin treatment and in maternal PKU females.

PKU-003 was a phase III, randomised, double-blind, placebo-controlled, multicentre study which enrolled patients eight years or older with known PKU and hyperphenylalaninaemia (blood phenylalanine level ≥450 micromol/L at screening). Patients had to have received at least seven out of

eight scheduled doses of sapropterin 10mg/kg per day in the PKU-001 study, which was an 8 day study, had a response to sapropterin (defined as a reduction in blood phenylalanine level of ≥30% from baseline) in the PKU-001 study and were willing to continue their current diet unchanged while participating in the PKU-003 study (it was not necessary to adhere to a strict low-phenylalanine diet). Patients were randomised equally to six weeks of treatment with oral sapropterin 10mg/kg once daily (100mg soluble tablets), or placebo and were stratified by blood phenylalanine concentration at screening (<600 micromol/L or ≥600 micromol/L) and study site.[2-4] The primary outcome measure was the change in blood phenylalanine levels from baseline to week 6 and was analysed in randomised patients that received one dose of study medicine. This excluded one patient, who was unable to comply with the study schedule, who had been randomised to sapropterin. [2, 5]

The mean change (standard deviation, SD) in blood phenylalanine concentration from baseline to week 6 in the sapropterin (n=41) and placebo (n=47) groups respectively were; -236 (SD 257) micromol/L and +2.9 (SD 239) micromol/L.[2, 5] Using an analysis of covariance method, the estimated difference between the treatment groups was -245 (SD 52) micromol/L, p<0.001.[2] Important secondary outcomes are described in table 1.

Table 1. Important secondary outcomes of the PKU-003 study. [1, 2, 5]

	Sapropterin	**Placebo**
Proportion of patients with at least a 30% reduction in blood phenylalanine concentration from baseline, %, (n)	44% (18/41) 95% CI: 28 to 60%	9% (4/47) 95% CI: 2 to 20%
	p=0.001	
Proportion of patients with blood phenylalanine concentration greater than 600 micromol/L at screening and less than this at 6 weeks, %, (n)[1, 5]	42% (13/31)	13% (5/38)
	p=0.012	

CI = confidence interval

In the sapropterin and placebo groups, 17% (7/41) and 26% (12/47) reported a change in their phenylalanine intake during the study.[2] No patient reported outcomes were recorded during PKU-003. PKU-004 was an open-label extension study of PKU-003: patients received doses of 5, 10 and 20mg/kg/day of sapropterin. The results highlighted a dose-dependent response in blood phenylalanine levels and supported the maintenance of effect of sapropterin over an additional 22 weeks. [5, 6]

The SPARK study was a phase IIIb, multicentre, open-label, randomised, controlled study which enrolled PKU patients less than 4 years old (at their scheduled day 1 visit), with at least two previous blood phenylalanine levels ≥400 micromol/L, had a previous response to a sapropterin test (≥30% decrease in phenylalanine concentrations following a 20mg/kg sapropterin challenge of at least 24 hours), dietary phenylalanine tolerance consistent with the diagnosis of PKU, good adherence to dietary treatment/recommendations, and maintenance of blood phenylalanine levels within the therapeutic target range (120-360 micromol/L) for 75% of assessments over a 4-month period prior to screening.[7-9] Randomisation was stratified by age group: <12 months, ≥12 months to <24 months, and ≥24 months to <48 months. Patients were randomised equally to 26 weeks of treatment with oral sapropterin 10mg/kg once daily plus a phenylalanine-restricted diet, or to a phenylalanine restricted diet only. Patients could have the dose of sapropterin increased to 20mg/kg daily after 4 weeks, if phenylalanine tolerance had not increased by 20% from baseline.[7, 9] Adjustments of dietary phenylalanine were made every two weeks following an algorithm and a study diet diary was used to

record and assess adherence to the phenylalanine restricted diet.[7] The primary outcome was an improvement in dietary phenylalanine tolerance at week 26 of treatment in the intention-to-treat population. Dietary phenylalanine tolerance was defined as the prescribed daily amount of phenylalanine (mg/kg/day) that could be ingested while maintaining mean blood phenylalanine concentrations within a target range of 120 to 360 micromol/L. [7-9] The adjusted mean phenylalanine tolerance at week 26 (based on prescribed dose) was higher in the sapropterin plus phenylalanine restricted diet group (n=27) than in the phenylalanine restricted diet only group (n=29): 80.6mg/kg/day versus 50.1mg/kg/day, the adjusted difference between the two groups was 30.5mg/kg/day (95% confidence interval [CI]: 18.7 to 42.3), p<0.001.[7, 9] Important secondary outcomes of the SPARK study included the mean adherence to the phenylalanine restricted diet, as assessed by a 3-day diet diary, which was similar in both groups.[7] There were no statistically significant differences between the two treatment groups in terms of neuromotor development milestones and neurodevelopment status, and growth parameters (Body Mass Index, height, weight, head circumference) were stable in both groups during the study.[9]

PKU-006-part-two was a phase III, multicentre, double-blind, placebo-controlled study which enrolled PKU patients aged 4 to 12 years adhering to a phenylalanine restricted diet. Part-one of the study was an open-label screening of patients for response (≥30% decrease in phenylalanine concentrations and blood phenylalanine concentration ≤300 micromol/L) to sapropterin 20mg/kg/day over 8 days and part-two only included patients that had a response to sapropterin in part-one.[5, 10] In part-two of the study patients were randomised, 3:1 to ten weeks of treatment with sapropterin 20mg/kg/day (n=33), supplied as 100mg sapropterin dihydrochloride soluble tablets once daily, or placebo (n=12) with all patients maintaining a phenylalanine restricted diet. Randomisation of patients was stratified by mean blood phenylalanine concentration, <300 or ≥300 micromol/L, in the six months prior to enrolment. If phenylalanine blood concentration was adequate (<360 micromol/L) following three weeks of treatment patients received a phenylalanine supplement. Patients were prescribed an additional phenylalanine supplement based on a defined algorithm every two weeks after week three, if blood phenylalanine concentrations allowed. The primary outcome was the daily phenylalanine supplement tolerated at week 10 compared to week 0 in the sapropterin treated group while maintaining blood phenylalanine concentration <360 micromol/L.[10] Sapropterin was associated with a statistically significant increase in mean tolerated phenylalanine supplement at week 10 from week 0: 20.9mg/kg/day versus 0mg/kg/day, p<0.001. In patients treated with placebo there was no statistically significant difference in mean tolerated phenylalanine supplement at week 10 from week 0. Secondary outcomes included an analysis of variance and an analysis of total dietary phenylalanine intake (dietary phenylalanine intake plus total phenylalanine supplement taken): results from both analyses were in line with the results for the primary outcome. [10]

Phenylketonuria Demographics, Outcomes, and Safety (PKUDOS) is a voluntary observed phase IV study in the United States, designed to assess 15 years of safety and efficacy outcomes on PKU patients of all ages treated with sapropterin and was initiated in 2008. To be eligible for entry in to the study patients were required to have a diagnosis of PKU and to previously or currently take sapropterin or plan to commence sapropterin within 90 days of enrolment. Assessments were conducted according to clinical practice at the participating site. Of the 1189 patients eligible for an interim analysis in June 2013 the majority received a dose of 20mg/kg/day oral sapropterin throughout the study. Sapropterin was associated with a 25 to 34% reduction in blood phenylalanine levels from baseline in patients with one to six years of continuous treatment (n=504), p<0.001; for patients who had received short term sapropterin (≤3 months) (n=211) there was no statistically significant change in blood phenylalanine levels from baseline. The proportions of patients that were sapropterin responsive (defined as ≥20% reduction in blood phenylalanine within three months of commencing treatment) were 71% in the continuous use group and 27% in the short term use group. It is difficult to draw conclusions on the reported changes in prescribed dietary phenylalanine and actual dietary phenylalanine from baseline but they appear to show a trend for increased phenylalanine intake with sapropterin treatment in the continuous use group.[11]

Maternal Phenylketonuria Observational Programme (PKUMOMS) is a sub-registry of PKUDOS registry. Data are available for 21 completed pregnancies from 18 women. 14/16 of pregnancies from sapropterin-treated women were live births compared to 3/5 from women who were exposed to sapropterin prior to pregnancy, but not during pregnancy. Two spontaneous abortions occurred in both groups. When median blood phenylalanine concentrations were maintained at <360 micromol/L, 75% of pregnancy outcomes were reported as normal as compared to 40% when median blood phenylalanine levels were >360 micromol/L.[12]

Summary of evidence on comparative safety

The safety of sapropterin has been evaluated over more than 10 years and safety data continues to be recorded in ongoing registries. Overall, sapropterin has been well tolerated.[5, 9]

In the PKU-003 study, no patient withdrew from the study due to an adverse event (AE) and no patient experienced a serious AE. The following were reported for the sapropterin (n=41) and placebo (n=47) groups respectively; treatment related AEs: 20% versus 23%, upper respiratory tract infection: 17% versus 28%, headache: 10% versus 15%, vomiting: 5% versus 9%, diarrhoea: 5% versus 6%, pyrexia: 5% versus 4%, abdominal pain: 2% versus 9%.[2]

In the SPARK study, all patients experienced at least one AE and no patients discontinued from the study due to an AE or had a serious treatment related AE. The following were reported for the sapropterin plus phenylalanine-restricted diet (n=27) and phenylalanine-restricted diet alone (n=27) groups; AEs related to sapropterin: 30% versus not applicable; serious adverse events: gastroenteritis: 3.7% versus 0%; rash: 3.7% versus 0%; stomatitis: 3.7% versus 0%; bronchiolitis: 0% versus 3.7% and bronchopneumonia: 0% versus 3.7%.[7, 9]

In the PKU-006-part-two study, 76% (34/45) of patients reported an AE. Treatment related AEs were reported by 27% (9/33) in the sapropterin group and 25% (3/12) in the placebo group. No serious adverse events were considered to be related to study treatment. The following were reported for the sapropterin and placebo groups; rhinorrhoea: 21% versus 0%, headache: 21% versus 8%, cough: 15% versus 0%, pharyngolaryngeal pain: 12% versus 8%, diarrhoea: 12% versus 0%, vomiting: 12% versus 0%, abdominal pain: 9% versus 8% and contusion: 9% versus 8%.[10]

PKU-008 was a phase IIIb, open-label, three year extension study of PKU-004 and PKU-006 in patients who were classified as responders to sapropterin treatment. Evaluation of the long term safety of sapropterin was the primary objective of the study. The study enrolled 111 patients, aged 4 to 50 years, who received once daily oral sapropterin 5mg/kg/day, 10mg/kg/day or 20mg/kg/day. There were no dietary restrictions for study entry, but patients were advised to follow local recommendations and safety assessments were conducted every 3 months. The majority of patients had a treatment interruption between studies.[13] The mean duration of exposure to sapropterin during the study was 658.7 days (SD 221.3 days). The mean duration of exposure to sapropterin including the studies preceding PKU-008 was 799 days (SD 237.5 days). Treatment related adverse events (AEs) were reported by 33% (37/111) of patients, severe AEs were reported by <1% (1/111), and 2.7% (3/111) of patients withdrew from the study due to adverse events.[13]

Some cases of hypophenylalaninaemia were reported and no treatment related deaths have been reported.[4, 5, 9, 11, 13, 14]

Summary of clinical effectiveness issues

Hyperphenylalaninaemia can lead to developmental and neurological (neuropsychological and neurocognitive function) impairment particularly in the early stages of life but also in adulthood. This may result in microcephaly, arrest in cerebral development, reduced intelligent quotient (IQ) scores; mental health, behavioural and emotional problems.[2] Depending on the mutation, hyperphenylalaninaemia can present with a range of phenotypes, these are commonly described as classical PKU (most severe), mild PKU and mild hyperphenylalaninaemia (least severe) which risk impaired brain function and neurological complications. The goal of treatment is to maintain phenylalanine levels within pregnancy or age-specified ranges. Maintaining phenylalanine levels within range is primarily achieved through adherence to a lifelong phenylalanine restricted diet and supplementation with phenylalanine-free amino acids and micronutrients to prevent the development of nutritional deficiencies. This management approach can be burdensome, unpleasant and associated with a reduction in quality of life: it is reported that by early adulthood at least 75% of patients are non-compliant with the dietary restrictions. [2, 7] Clinical experts consulted by SMC highlighted an unmet need for a treatment that supports normal metabolic function. Sapropterin is the first licensed medicine for the treatment of PKU and meets SMC orphan criteria.

Following the initial submission, the company requested that SMC considered sapropterin when positioned for use in the paediatric PKU population i.e. 0 to 18 year olds, uncontrolled (elevated phenylalanine with symptoms) and partially controlled (phenylalanine within target levels with presence of symptoms) who have been shown to be responsive to sapropterin treatment, and in maternal PKU females.

The PKU-003 study reported a statistically significant reduction in blood phenylalanine level associated with sapropterin over placebo in PKU patients, aged 8 years and older, known to respond to sapropterin and who were not required to adhere to a phenylalanine-restricted diet.[2] A statistically significant increase in phenylalanine tolerance was associated with sapropterin plus phenylalanine-restricted diet over phenylalanine-restricted diet (plus placebo in PKU-006-part-two). Blood phenylalanine levels were maintained within the target range in patients known to respond to sapropterin who were aged under 4 years in the SPARK study and aged 4 to 12 years in the PKU-006-part-two study.[7]

There were a number of limitations of the PKU-003 study: no details of nutritional or clinical impact of sapropterin were recorded and a larger proportion of patients in the placebo group reported changes in their diet during the study compared with the sapropterin group.[2] It is unclear why only 44% of all patients enrolled in the PKU-003 study had a response, having previously had a response in the PKU-001 study. Patients were only allowed to enter the pivotal studies if they had a prior response to sapropterin: this was assessed over 8 days in PKU-001 for entry to PKU-003, and PKU-006-part-one for entry to part-two, and over at least one day in the SPARK study. The SPC advises patients should have a one month test period.[1] In addition, a high proportion of patients included in PKU-003 had a high level of adherence to treatment which may reduce the generalisability of the results to the Scottish population. Limitations of the PKUDOS study include that the registry is voluntary, observational and uncontrolled; practice may vary across the study sites; data may be incomplete and not all data were verified.[11]

No patient reported outcomes were recorded in the PKU-003, PKU-006-part-two or SPARK studies. Patients in the sapropterin group of the SPARK study had a lower mean blood phenylalanine concentration (780 versus 880 micromol/L) and had a lower proportion of patients with classical PKU (blood phenylalanine concentration >1200 micromol/L) at baseline (18% [5/27] versus 24% [7/29]) compared with the control group.[7, 9]

While blood phenylalanine levels are a surrogate for hyperphenylalanaemia-associated neurological damage and are widely used in practice to manage the condition, robust data on longer-term outcomes following use of sapropterin are unavailable.

Maternal PKU syndrome can result when babies are exposed to high concentrations of blood phenylalanine in utero: exposure to high concentration can put the baby at significant risk of birth and developmental defects which would likely affect the individual throughout their whole life.[15] The data to support use of sapropterin in pregnancy is limited to registry programmes such as PKUMOMS.

Clinical experts consulted by SMC considered that sapropterin is a therapeutic advancement as it supports normal metabolic function in a proportion of patients with PKU. They noted that there would be some service implications associated with identification of patients suitable for ongoing treatment.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of sapropterin, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- PKU is a rare genetic disease resulting in high blood phenylalanine levels that can cause permanent brain damage in children and can impair cognitive and neuropsychological functioning in adults. Maternal PKU can result in non-viable pregnancies, birth defects and lifelong learning disability in the offspring.
- Patients with phenylalanine blood levels above the target range while adhering to a phenylalanine restricted diet have no alternative treatment options. Most patients are unable to adhere to the diet all of the time as most foods contain phenylalanine and obtaining or preparing appropriate food can be extremely challenging and time-consuming, particularly for symptomatic patients. The PKU diet may not provide patients with enough calories and patients regularly feel hungry. Some patients may also have complex relationships with food and develop eating disorders. Parents may fear the perception of poor care and social services intervention.
- Fear of maternal PKU and the associated risk of fetal damage may affect women's lives with reports of reduced ability to form intimate relationships, choosing not to have children and deciding to terminate pregnancies.
- Experience of sapropterin use in practice indicates that it can improve quality of life, physical and mental health. It can allow patients and families freedom from the burden of the restrictive diet and worry of causing long term brain damage.
- Patients who obtain a response to treatment with sapropterin may have significant improvements in their neuropsychological functioning with noticeable academic progress, development of social skills, and improved employability. In addition, depending on the degree of response to treatment, patients may be able to increase their natural protein intake or commence a normal diet without risk

Additional Patient and Carer Involvement

We received patient group submissions from Phed up and The National Society for Phenylketonuria (United Kingdom) Ltd (NSPKU). Phed up is an action group and NSPKU is a registered charity. Phed up has not received any funding from pharmaceutical companies in the past two years. NSPKU has also not received any funding from pharmaceutical companies in the past two years. Representatives

from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing sapropterin plus a phenylalanine restricted diet to a phenylalanine restricted diet alone in adult and paediatric patients of all ages with PKU for the treatment of HPA in patients who have been shown to be responsive to sapropterin treatment. The comparator appears to be appropriate. The patient population considered consists of a combination of 0 to 18 year olds uncontrolled (elevated phenylalanine with symptoms) and partially controlled (phenylalanine within target range but with presence of symptoms) who are shown to be responsive to sapropterin treatment, and those aged >18 years uncontrolled but responsive to sapropterin treatment. Following the initial submission, the company requested a selective positioning of 0 to 18 year olds, uncontrolled (elevated phenylalanine with symptoms) and partially controlled (phenylalanine within target range but with presence of symptoms), who are shown to be responsive to sapropterin treatment, and maternal PKU females. The results discussed relate to the proposed selective positioning.

The model consists of an initial 4-week decision tree representing a testing period whereby patients' response to sapropterin treatment is assessed with those achieving a ≥30% reduction in blood phenylalanine levels considered to be responders (based on SPC), and then moving into a Markov part of the model, with non-responders ceasing treatment with sapropterin. The company have not included the cost of sapropterin within this four week period on the grounds this will be borne by the company. It was assumed that 30% of patients would respond to sapropterin treatment in this testing period, which was based on clinical expert opinion. The Markov model includes health states consisting of controlled, uncontrolled, partially controlled, asymptomatic and death. The Markov model time horizon was 100 years, and a yearly cycle length was adopted.

Clinical data on the effectiveness of sapropterin plus diet versus diet alone were derived from a sub-set of data for patients receiving continuous sapropterin and those who did not respond to treatment but moved to diet alone from the PKUDOS study, a phase 4 longitudinal observational study with data collected in PKU patients aged 0 to 71 years.[11] The patients in the two groups were matched based on age and baseline phenylalanine. Transition probabilities in the model for each treatment arm were derived from 6 years of data from this registry. The transition probabilities based on this data are applied for patients aged 1 to 6 years after which a standard mortality rate is assumed, and then again at age 19 to 24 with standard mortality rates only applied after this time in the model. It also appears from the model that the positioning of treating uncontrolled or partially controlled patients with sapropterin means that once a patient moves into the controlled state they are assumed to cease treatment and no further medicine cost is incurred.

Health-related quality of life health state utilities were estimated by clinicians based on the EuroQoL five dimensions (EQ-5D) with different utilities assigned for children (EQ-5D-Y) and adults. Different utilities were also estimated for males and females in the uncontrolled health state (lower for females).

Medicine acquisition, disease monitoring and management costs were included in the economic analysis. Costs for medicines acquisition for sapropterin, diet costs, disease monitoring and management costs (GP, outpatient and specialist visits) and hospitalisation costs were included. Resource use estimates were largely based on expert clinical opinion. The company assumed that the natural intake of protein would be increased with sapropterin treatment hence reducing the need for protein supplements and the costs associated with these for the sapropterin cohort. In the base case a 70% natural protein intake increase with sapropterin based on an analysis of PKUDOS data was

assumed to correspond to a 70% reduction in costs of protein supplements in the sapropterin cohort.[16] No costs or disutilities have been included for adverse events.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision but due to company requirements for commercial confidentiality no incremental cost-effectiveness ratios (ICERs) can be presented.

One way sensitivity analysis indicated the ICERs were sensitive to variation in health state utilities. Scenario analysis using the Short Form-six dimensions (SF-6D) with clinical experts to generate utilities for adults did not have a significant impact on the ICER, however capping controlled state utilities at the population norm increased the ICER. The ICER also substantially increased when assuming all 0 to 18 year old patients are treated regardless of control status. Further sensitivity was also shown to the estimate of natural protein intake increase and consequent cost reduction in the sapropterin cohort; compared to the base case of 70%, a 100% increase and protein cost supplement reduction improved the ICER significantly, whilst scenarios with a 50% or 30% intake increase/cost reduction resulted in large increases in the sapropterin ICER.

There are several weaknesses and uncertainties with the economic analysis:

- The company requested a selective positioning for sapropterin which includes a subgroup of maternal PKU females but it should be noted that no specific economic analysis pertaining to this population was presented.
- There was a lack of transparency in the submission regarding the positioning of sapropterin to treat only those patients who were defined as uncontrolled or partially controlled, and the handling of this in the economic analysis. From investigation of the economic model it appears patients only incur a sapropterin medicine cost whilst not in the controlled states ('asymptomatic' or 'partially controlled'), implying that treatment ceases when moving into this state. However, it also appears that it is assumed there would be no loss of subsequent benefit (i.e. QALYs) when patients move into the controlled state but no longer receive sapropterin treatment, which seems unlikely. Hence, the ICERs are likely to be underestimated because of this. The company in response to a question stated that a PKU patient is in need of treatment for life in order to control their phenylalanine levels within the target range, hence the plausibility of the positioning requested to treat only uncontrolled patient, therefore to cease treatment in those with control (at least according to the economic model) is highly questionable.
- The estimated natural protein intake and reduction in the use of protein supplements and hence cost of diet in the sapropterin arm leads to significant cost offsets. There is uncertainty over the cost reduction estimated and the extent to which such cost savings can be realised in practice. Scenario analysis indicated that the ICER is sensitive to the level of cost offsets estimated.
- PKUDOS registry data has been used as the basis of the effectiveness data but none of the other sapropterin clinical or observational study evidence reported in section 3 of the submission has been utilised. It is not known to what extent this introduces bias into the treatment effectiveness evidence used in the economic analysis. There are concerns over the strength and generalisability of the registry data and the methods used for matching patients across the sapropterin plus diet and diet alone groups from the PKUDOS registry has not been clearly presented.
- There were a number of issues in terms of the model structure and operation. For example, examination of the economic model suggests that the way transition probabilities are being applied (only for first 6 years for the 0 to 18 year population, and for years 19 to 24 for the adult population) with only mortality risk applied outside of these years could be biased in favour of

sapropterin as a higher proportion of sapropterin relative to diet alone patients appear to remain in the controlled state. The approach adopted may be associated with underestimated ICERs. In addition, including the decision tree part of the model appears unnecessary as it does not impact on the model costs and outcomes, and means that in order to keep the cohort size the same for both the sapropterin plus diet and diet alone treatment arms in the Markov phase the assumption of 30% responders to sapropterin after the testing period is applied to both arms. This lacks plausibility and hence it would have been simpler and more transparent to start the model with the Markov model.

- The utilities used in the model are highly uncertain, with some utility estimates lacking face validity (e.g. 0.96 for controlled states in adults and children). Scenario analysis capping the utilities at population norms increased the ICER.

The Committee considered the benefits of sapropterin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as sapropterin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence including the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept sapropterin for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

European guidelines to optimise the care of patients with PKU entitled 'Key European guidelines for the diagnosis and management of patients with phenylketonuria' were published in 2017 by European experts sponsored by European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU).[15] Management of PKU aims to decrease blood phenylalanine concentration to within appropriate age-based ranges. Low phenylalanine-diet, restricting the intake of natural protein containing phenylalanine, low protein foods and phenylalanine-free amino acids supplements with added vitamins and minerals, are the mainstay of PKU management. Some patients with PKU respond to tetrahydrobiopterin (BH4), sapropterin dihydrochloride is the licensed version of this. All patients should be tested for BH4 responsiveness through genotyping or BH4 loading, and BH4 should only be prescribed in patients with proven long term BH4 responsiveness; described in the guidelines as a 100% increase in intake of the amount of natural protein, or maintaining phenylalanine levels in target range more than 75% of the time, during a 6 month treatment trial with BH4. If blood phenylalanine levels are maintained in range; natural protein intake can be increased, supplements decreased and BH4 adjusted accordingly; if phenylalanine blood levels are higher than the target range, with a lack of response to increased BH4 dose, then BH4 should be stopped. Discontinuation of BH4 should be considered if nutritional status deteriorates. During pregnancy, treatment with BH4 should be considered in women know to be responders and only if dietary treatment alone is unsuccessful.

Casein glycomacropeptide or large neutral amino acids are used in some countries, primarily non-European, but further research is required to ascertain safety and efficacy profiles of these treatments.[15]

Additional information: comparators

There are no comparator treatments for this indication.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Sapropterin dihydrochloride	5 to 20mg/kg once daily orally	21,739 to 101,448

Costs from BNF on 30 March 2018. Costs do not take any patient access schemes into consideration. Adult doses have been estimated using a body weight of 70kg. Costs for children will be lower.

Additional information: budget impact

The submitting company estimated there would be 122 patients eligible for treatment with sapropterin in year 1, rising to 128 patients in year 5 to which confidential estimates of treatment uptake were applied. It should be noted that the eligible patient numbers did not relate specifically to the proposed positioning considered by SMC and included a wider patient population.

SMC is unable to publish budget impact estimates due to commercial in confidence issues.

*Other data were also assessed but remain commercially confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.