

## Review Article

# Adjusting diet with sapropterin in phenylketonuria: what factors should be considered?

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### Abstract

The usual treatment for phenylketonuria (PKU) is a phenylalanine-restricted diet. Following this diet is challenging, and long-term adherence (and hence metabolic control) is commonly poor. Patients with PKU (usually, but not exclusively, with a relatively mild form of the disorder) who are responsive to treatment with pharmacological doses of tetrahydrobiopterin (BH<sub>4</sub>) have either lower concentrations of blood phenylalanine or improved dietary phenylalanine tolerance. The availability of a registered formulation of BH<sub>4</sub> (sapropterin dihydrochloride, Kuvan<sup>®</sup>) has raised many practical issues and new questions in the dietary management of these patients. Initially, patients and carers must understand clearly the likely benefits (and limitations) of sapropterin therapy. A minority of patients who respond to sapropterin are able to discontinue the phenylalanine-restricted diet completely, while others are able to relax the diet to some extent. Care is required when altering the phenylalanine-restricted diet, as this may have unintended nutritional consequences and must be undertaken with caution. New clinical protocols are required for managing any dietary change while maintaining control of blood phenylalanine, ensuring adequate nutrition and preventing nutritional deficiencies, overweight or obesity. An accurate initial evaluation of pre-sapropterin phenylalanine tolerance is essential, and the desired outcome from treatment with sapropterin (e.g. reduction in blood phenylalanine or relaxation in diet) must also be understood by the patient and carers from the outset. Continuing education and support will be required thereafter, with further adjustment of diet and sapropterin dosage as a young patient grows.

**Key words:** Phenylketonuria; Sapropterin; Phenylalanine; Nutrition; Inherited metabolic disorders

Traditionally, in phenylketonuria (PKU), a lifelong low-phenylalanine diet, supplemented with a phenylalanine-free protein substitute, has been the cornerstone of treatment. Undoubtedly, diet is a highly successful treatment, but it does require discipline from patients and organisational skills and commitment from

carers. Not surprisingly, the severity of the dietary intervention renders dietary adherence an issue for some patients, and any therapy that will help ease dietary management is welcomed.

Sapropterin dihydrochloride is the biologically active synthetic form of tetrahydrobiopterin (BH<sub>4</sub>), the naturally

**Abbreviations:** BH<sub>4</sub>, tetrahydrobiopterin; PAH, phenylalanine hydroxylase; PKU, phenylketonuria.

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occurring, essential cofactor for the enzyme phenylalanine hydroxylase (PAH). Kuvan® (Merck Serono, Geneva, Switzerland; BioMarin Pharmaceutical, Inc., Novato, CA, USA) is the only commercial, registered formulation of sapropterin available for prescription (for clarity, the term, 'sapropterin', refers exclusively to this commercial formulation in the present study). Sapropterin lowers blood phenylalanine concentrations and improves phenylalanine tolerance in a subset of patients with PKU and is the first pharmacological treatment approved for this indication<sup>(1,2)</sup>. It is used either as an adjunctive therapy to a low-phenylalanine diet, or it may provide an alternative to diet. PKU may be severe (little or no activity of PAH), and when untreated, it is characterised typically by very high blood phenylalanine concentrations; or it may be mild or moderate (in which there is some residual activity of PAH), and when untreated is characterised by lower blood phenylalanine concentrations. Response to BH<sub>4</sub> (including sapropterin) treatment is usually more pronounced in patients with a mild or moderate PKU phenotype. Approximately 20–60% of patients have been shown to achieve a ≥30% reduction in blood phenylalanine concentration with sapropterin or the previous, unregistered formulation of BH<sub>4</sub><sup>(1–6)</sup>.

The European experience with sapropterin as an adjunct to diet therapy is limited, and there are no agreed strategies for its use in conjunction with diet. It may therefore be some time before adequate knowledge and experience supports a consensus on the use of sapropterin by all professionals in Europe. Accordingly, it is important to begin an open debate on the implications for PKU dietary management when sapropterin is used as an adjunct to treatment. Therefore, the purpose of the present review is to give practical guidance for the optimisation of diet treatment in patients treated with sapropterin dihydrochloride and highlight areas that require further research.

### Choosing potential patients for sapropterin therapy

Ideally, to ensure equity of treatment for patients with PKU who require a low-phenylalanine diet, regardless of age, genotype and dietary adherence, they all should be offered testing for responsiveness to sapropterin<sup>(5)</sup>. However, this is unlikely to occur at the present time for several reasons. For example, the high cost of the drug compared with dietary treatment is a barrier to its use in some countries, and criteria may be required for identifying patients at the highest priority within the BH<sub>4</sub>-responsive patient population. Potential criteria include the presence of psychological difficulties caused by diet, patients considered for intervention by social services, eating disorders or patients in a poor nutritional state<sup>(7–9)</sup>. Conversely, sapropterin treatment should not be considered as the answer to, or a reward for, poor dietary compliance, especially as the patient may still not comply with a less restrictive diet after a therapeutic response to sapropterin. Some experts only recommend testing patients with a genotype that predicts a high likelihood of BH<sub>4</sub>-responsive PKU<sup>(10)</sup>, although genotyping of PAH alone is insufficient to predict the degree of BH<sub>4</sub> responsiveness in an individual patient<sup>(2,5,11,12)</sup>. However, knowledge of a genotype

conferring little or no residual activity of PAH (e.g. in a patient homozygous for R408W) greatly reduces the likelihood of a therapeutic response to sapropterin and may provide useful information to guide decisions on whether to apply a sapropterin loading test.

Sapropterin may have an important role in pregnancy in the future<sup>(13)</sup>. Although dietary phenylalanine restriction is currently the treatment of choice in pregnant women with PKU, the European prescribing information for sapropterin acknowledges that sapropterin may be considered in pregnancy, due to the clear and proven danger to the fetus from maternal hyperphenylalaninaemia, but 'only if strict dietary management does not adequately reduce blood phenylalanine levels'. Sapropterin has been used occasionally, during preconception and pregnancy, at low doses (50–100 mg/d in the first trimester to 300–400 mg/d in the third trimester)<sup>(14)</sup> and mostly in women with poor control on diet alone. Reports of successful pregnancy outcomes, with normal infant neurological and physical development, have been published<sup>(14,15)</sup>.

### Pre-sapropterin patient/carer interview

It is essential to try to manage patient/carer expectations regarding sapropterin. In particular, patients and carers must understand the likelihood of sapropterin responsiveness and be briefed carefully on the potential benefits of the drug. Careful explanation is also required on how treatment with sapropterin is introduced, how its effectiveness is assessed, how diet will be adjusted, the impact of illness on blood phenylalanine concentrations, what monitoring will be required and the likelihood of its continued long-term use. In addition, the possibility of an agreed patient contract can be considered, which outlines the conditions under which sapropterin may be withdrawn and full dietary treatment recommenced.

### Pre-sapropterin dietary work-up

An unchanged daily phenylalanine allowance may have been prescribed for years if blood phenylalanine concentrations remain within the target range, even though an individual's total phenylalanine requirements may have increased as a consequence of growth. This may be especially important in patients with non-PKU hyperphenylalaninaemia who are not prescribed a phenylalanine-free protein substitute, but who may still restrict their intake of natural protein, resulting in protein insufficiency<sup>(16)</sup>. Therefore, it is important to establish actual phenylalanine tolerance before starting sapropterin (carers or patients should prospectively and accurately record all sources of dietary phenylalanine over 3 d).

Knowledge of day-to-day variability in blood phenylalanine concentrations, based on fasting blood samples, is important when assessing sapropterin therapy. Fasting blood phenylalanine concentrations should be monitored weekly for at least 4 weeks before the sapropterin response test to give a good indication of overall blood phenylalanine control on diet only.

Issues with dietary treatment, e.g. hunger and adherence, as well as nutritional status (growth, undernutrition, body fat

composition and micronutrient status) and haematological and biochemical nutritional intake<sup>(17)</sup> should be documented.

### Sapropterin oral response test

Several protocols for BH<sub>4</sub> loading tests for use in the diagnosis of BH<sub>4</sub>-responsive PKU have been described, with initial doses of 10–20 mg sapropterin/kg per d<sup>(5,18)</sup>. A blood phenylalanine concentration of >400 μmol/l<sup>(19)</sup> at the start of the test is generally regarded as a pragmatic compromise between a high enough level to permit ready detection of a treatment effect of sapropterin, while remaining reasonably close to lower goal values for younger patients. A reduction in blood phenylalanine of >30% is generally regarded as a response to treatment, although also the European prescribing information for sapropterin recognises the freedom of the prescribing physician to set a therapeutic blood phenylalanine goal for an individual patient.

The rate of response to BH<sub>4</sub> varies, and slow responders (patients who do not respond with a substantial reduction in blood phenylalanine within 48 h of the initiation of treatment) make up 20–30% of cases<sup>(9,10,20,21)</sup>. The duration of the sapropterin response test has varied from 8 h to 1 week, with an extension to 4 weeks<sup>(5)</sup>.

### Adjusting the low-phenylalanine diet

The main goal of sapropterin treatment is to lower blood phenylalanine concentrations, increase dietary phenylalanine tolerance<sup>(22)</sup> and subsequently reduce or eliminate the need for a phenylalanine-free protein substitute. Ultimately, the degree of diet liberalisation will depend on the magnitude of the change in blood phenylalanine/phenylalanine tolerance and the target blood phenylalanine concentration.

Some patients, especially those with a milder PKU phenotype, may demonstrate a large and rapid decrease in blood phenylalanine, associated with a marked increase in their tolerance of dietary phenylalanine<sup>(23)</sup>, although further evaluation in randomised controlled trials is required to validate this. Given the variable therapeutic response to sapropterin in clinical trials, any protocol for phenylalanine introduction should be individually determined.

A minority of patients with good phenylalanine tolerance on sapropterin will be able to stop their natural protein restriction and are likely to tolerate rapid introduction of dietary phenylalanine<sup>(21)</sup>. Most responders will still require some dietary restriction but have a two- to threefold increase in dietary phenylalanine intake<sup>(8,24)</sup>. Any increase in dietary intake must be carefully titrated with the measurement of blood phenylalanine concentrations and adjustment of the sapropterin dose, where appropriate.

A variety of protocols have been suggested for increasing dietary phenylalanine. Lambruschini *et al.*<sup>(25)</sup> increased dietary phenylalanine by 200 mg/d per week in patients with mild or moderate PKU. Singh *et al.*<sup>(26)</sup> suggested an introduction of 10 mg sapropterin/kg per d, although a more conservative introduction may be a standard additional dose of 100 mg/d, in combination with regular monitoring of blood phenylalanine

concentrations. Dietary phenylalanine should continue to be increased, systematically, by the same amount (i.e. 100 mg/d) every 7 d, but only until blood phenylalanine concentrations start to escalate beyond target blood phenylalanine concentrations. Increasing phenylalanine by an individually determined percentage of the original daily tolerated phenylalanine intake represents an alternative option.

In order to establish accurate phenylalanine tolerance, any additional dietary phenylalanine should only be introduced under stable conditions. A new baseline blood phenylalanine concentration may be attained approximately 7 d after adjusting the diet, although further evidence is required to establish whether a longer period of observation would be better. Some patients may have a delayed increase in blood phenylalanine concentrations, and so it may be challenging to establish definitive phenylalanine tolerance when additional phenylalanine is added too quickly. Careful dietary records should be kept during the dietary phenylalanine introduction phase.

### Source of dietary phenylalanine during the introduction phase

Without careful attention, it is possible that an excess of dietary phenylalanine may be given inadvertently during the introduction and adjustment phase. Therefore, consideration should be given to the type of phenylalanine source initially introduced (i.e. animal or vegetable protein sources). If high-protein foods are introduced, but then have to be withdrawn, this is likely to be difficult where an individual has become accustomed to their taste. Some dietitians initially introduce only milk or egg protein<sup>(26,27)</sup> or even L-phenylalanine powder, providing a straightforward and quantitative approach to assessing the new phenylalanine tolerance without having to calculate the phenylalanine content of variable food sources. The use of these protein sources should aid the patient's ability to return to their previous dietary regimen if necessary<sup>(18)</sup>.

Once the dietary phenylalanine introduction phase is complete, any additional dietary phenylalanine should be tolerated indefinitely, provided the sapropterin dose is titrated in accordance with blood phenylalanine concentrations and adherence to drug and diet is satisfactory (the European prescribing information for sapropterin states that the sapropterin dose is 'adjusted, usually between 5 and 20 mg/kg per d, to achieve and maintain adequate blood phenylalanine levels as defined by the physician'). Although it is assumed that patients would prefer to eat all natural sources of protein, some may be hesitant to try high-protein foods, because they have been taught to avoid these foods in the past.

### Phenylalanine-free protein substitute adjustment

Some patients may struggle with the taste and daily routine of protein substitute and may identify a reduction in its dosage as a goal of sapropterin treatment. Previously, few studies have demonstrated that removal of the substitute from the diet may be possible for half or more of BH<sub>4</sub>-treated patients with mild or moderate PKU, including treatment periods

measured in years<sup>(8,23,25)</sup>. The following two criteria should be met before there is any reduction in the dosage of the protein substitute: (1) the total protein equivalent intake (from natural sources and protein substitute) should supply, as a minimum, the safe level of protein intake defined by the WHO<sup>(28)</sup>; (2) all vitamin and mineral requirements should be met.

In patients on dietary treatment only, protein substitute may provide as much as 85% of the total protein requirement. In sapropterin-responsive patients, it is assumed that protein equivalent from protein substitute will be exchanged, gram-per-gram, for natural dietary protein<sup>(7)</sup>. However, phenylalanine-free protein substitutes have many functions in addition to supplying non-phenylalanine essential amino acids. They contribute to: (1) lowering of blood phenylalanine concentrations<sup>(29–31)</sup> (probably associated with anabolism and competition with phenylalanine for absorption from the gut); (2) providing an important source of dietary tyrosine; (3) providing some essential fatty acids and DHA. An alternative approach to protein substitute administration is treatment with large, neutral amino acid supplementation, which is believed to reduce phenylalanine transport across the blood–brain barrier<sup>(32,33)</sup>. The influence of treatment with sapropterin on the ratio of phenylalanine to other large, neutral amino acid or the need for continued prescription of large, neutral amino acid supplements remains to be determined.

Because of the valuable role of a protein substitute, some experts consider that it should always be administered<sup>(26)</sup>. It may be particularly important during illness to help control blood phenylalanine concentrations, and it is essential that patients remain accustomed to its taste for use during illness, pregnancy or if sapropterin treatment is stopped.

Most protein substitutes are enriched with micronutrients. Reducing the dose, even with improved phenylalanine tolerance, may compromise intake of vitamins and trace minerals, if the nutritional quality of the extra dietary phenylalanine sources is limited. If few natural protein sources are eaten, an additional dietary supplement of micronutrients is desirable. Therefore, either a separate vitamin and mineral supplement should be prescribed or there may be a need for new protein substitutes for use with sapropterin, containing a higher concentration of vitamin and minerals relative to phenylalanine-free protein, to compensate for a partial withdrawal of the substitute.

### Special low-protein foods

Sapropterin-responsive patients who experience a two- or threefold increase in phenylalanine tolerance should reduce their dependence on special low-protein foods such as bread, biscuits and pasta, but this will be determined by overall phenylalanine tolerance, appetite and energy requirements. Any reduction in the use of special low-protein foods should save the family time because of less need for special food preparation.

### Nutritional quality of diet

Some patients accustomed to eating a low-phenylalanine diet may still choose to eat a limited range of foods and may be at

risk of developing nutrient deficiencies if they transfer to a normal diet without continued nutritional support with vitamin and mineral supplementation. However, when eleven patients were treated for 1 year with BH<sub>4</sub>, and a normal diet was introduced and protein substitute stopped, no differences in the nutritional marker status were observed, and all were within target reference ranges. Interestingly, plasma levels of Se significantly increased without any significant changes in the daily Se intake during that year<sup>(25)</sup>.

### Patient/carer education

Patients/carers require education about healthy 'normal' nutrition, diet and lifestyle if they are sapropterin responsive. They will need information about the protein and nutritional content of higher-protein foods, the principles of weight control, illness management and the continued need for adherence with the new treatment regimen, and the regular monitoring of blood phenylalanine concentrations. There have been no reports to date describing dietary patterns, range of foods eaten and quality of diet in BH<sub>4</sub>-responsive patients.

### Monitoring

In general, monitoring during sapropterin treatment follows the same principles as outlined in the dietary management of PKU. Blood phenylalanine and tyrosine concentrations should be monitored frequently during any dietary manipulations due to the highly variable responses to sapropterin. Transiently low blood phenylalanine concentrations (<26 μmol/l) may occur if insufficient dietary phenylalanine is given<sup>(2)</sup>. Weekly testing should be a minimum requirement during stabilisation of diet after introducing sapropterin, although some recommend daily testing (where laboratory support for this is available). An assessment of diurnal variation in blood phenylalanine is helpful, as a high intake of dietary phenylalanine with a reduced dose of protein substitute is likely to lead to an increase in phenylalanine concentration during the day. Once stability in blood phenylalanine concentrations and dietary phenylalanine tolerance is achieved, blood phenylalanine monitoring may be carried out according to the local guidelines.

Reassuringly, it has been reported that tyrosine concentrations remain unchanged with BH<sub>4</sub> treatment<sup>(24,34)</sup>. A reduced variability in phenylalanine:tyrosine ratios in BH<sub>4</sub>-responsive patients, compared with age-matched non-responsive PKU patients, has also been documented<sup>(34)</sup>.

Dietary intake, growth or BMI (depending on age) should be checked at least monthly until food patterns have stabilised, to ensure that all nutritional requirements are met and normal growth or weight is achieved, followed by a return to the usual monitoring guidelines for the age group. It is essential that biochemical/haematological nutritional markers be assessed annually in the long term, similar to when PKU is treated by diet only<sup>(17)</sup>. Table 1 shows a number of measurements that may facilitate optimisation of nutrition, although tests for some metabolites may be expensive, such as glutathione

peroxidase, Zn, Se or fatty acids, and may be considered as unessential to the routine management of PKU.

Quality of life should also be monitored: although there are no specific assessment tools for patients with PKU, it is important to document any practical and social difficulties associated with PKU, diet and treatment. Information on social outcome relating to school, work, friendships and general satisfaction with life is helpful. It is also important to monitor the impact of sapropterin and a relaxed dietary approach on neurocognitive function and quality of life. Measurements should be assessed at baseline and then at regular intervals during sapropterin treatment.

**Potential issues with sapropterin**

*Growth*

Impaired growth has been reported in some but not all studies in diet-treated children with PKU<sup>(35)</sup>. Longitudinal data with BH<sub>4</sub> treatment are limited, but a group of five infants given sapropterin for 24 months maintained growth, length and head circumference within the normal ranges for age and sex<sup>(24)</sup>. All had normal mental and motor development.

*Weight management*

While unhealthy foods may be chosen by patients prescribed a stringent or relaxed diet, greater dietary freedom may result in higher consumption of high-carbohydrate and fatty meals. Overweight has been reported in children with PKU<sup>(36)</sup>, and an increase in adiposity has been reported in six of eleven patients responsive to BH<sub>4</sub> and eating a normal diet<sup>(25)</sup>. It is essential to continue monitoring dietary intake and weight, and to give appropriate dietary advice, based, if possible, on analysis of body composition and physical activity patterns.

*Illness*

Blood phenylalanine typically increases with catabolic stress (e.g. fever and trauma), and increased blood phenylalanine has been reported in febrile sapropterin-treated or diet-treated patients with PKU<sup>(7,23,24)</sup>. It may be necessary to increase the dose of BH<sub>4</sub> during illness (up to a maximum dosage of 20 mg sapropterin/kg per d), to reintroduce protein substitute or to reduce dietary phenylalanine intake temporarily<sup>(7,37)</sup>. Reintroduction of diet may be exceptionally difficult during illness, especially for younger patients and particularly if the patient had become accustomed to a normal diet.

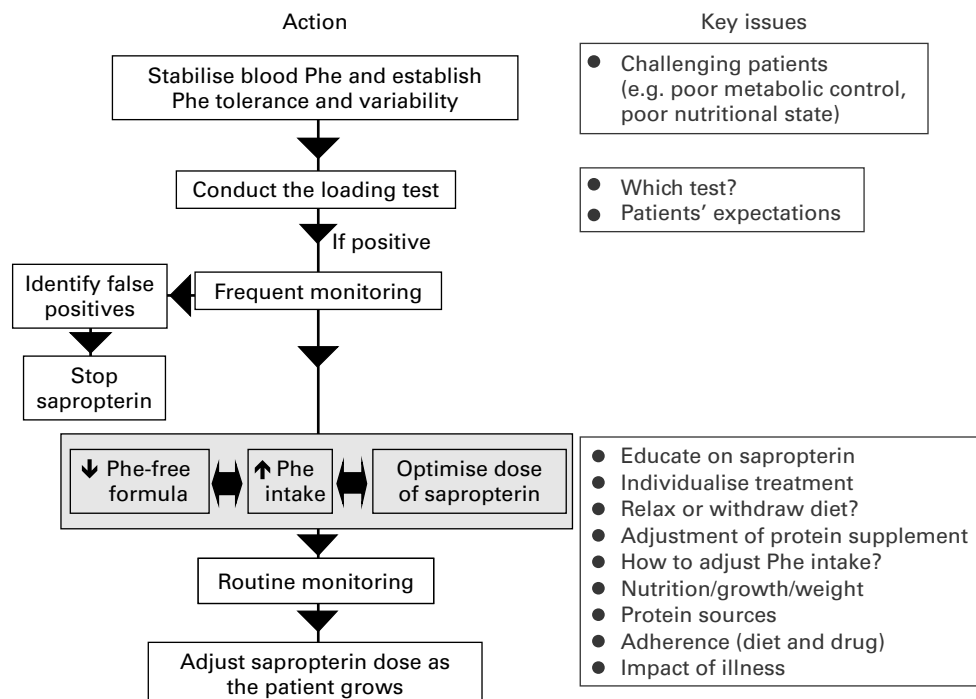
*Long-term management with sapropterin*

There is no definition of acceptable adherence to sapropterin and diet. Sapropterin dihydrochloride is a relatively new treatment, and data on long-term management are limited. A preliminary report of a long-term extension study with sapropterin has demonstrated compliance (by tablet counting) of >80% in 96% of patients (n 106) and of >60% in 98% of patients (n 109); mean blood phenylalanine concentration

**Table 1.** Assessment of nutritional status before and during the use of sapropterin with diet\*

Dietary intake 3 d self-recorded dietary assessment	Anthropometric measurements Height/length Weight Body fat composition Head circumference (up to 3 years of age) Measurements can be compared with national growth charts, converted to z scores, and BMI calculated from height and weight	Nutritional haematological–biochemical markers Fasting quantitative amino acids Albumin (plasma) Transferrin (plasma) Fe (plasma/serum) Ferritin (plasma) Hb (whole blood) Haematocrit (whole blood) Se (serum/plasma) Glutathione peroxidase Zn (plasma/serum) Ca (plasma/serum) Vitamin B <sub>12</sub> (plasma) Fatty acids Total amino acid profile
Minimum frequency of assessment Pre-sapropterin: once Post-sapropterin and phenylalanine introduction: monthly Post-stabilisation with sapropterin: 6 months	Pre-sapropterin: once Post-sapropterin and phenylalanine introduction: monthly Post-stabilisation with sapropterin: 2–3 months in children aged <5 years; 6 months in children aged ≥5 years	Pre-sapropterin: once Post-sapropterin and phenylalanine introduction: 6 months post-introduction Post-stabilisation with sapropterin: annually

\* Adapted from Acosta<sup>(17)</sup>.



**Fig. 1.** Summary of key actions and issues relating to combining diet and sapropterin therapy for patients with phenylketonuria. Frequent monitoring is recommended weekly. Routine monitoring is carried out according to the usual protocol employed by the clinic. Phe, phenylalanine. See text for a full discussion of the issues summarised here.

was decreased from a baseline value of 614 to 504.6 (SD 316.3)  $\mu\text{mol/l}$  at 3 months and remained between 485 and 530  $\mu\text{mol/l}$  thereafter<sup>(38)</sup>. However, individual cases of poor adherence have been described<sup>(4)</sup>, and only 60% of patients have reported taking all doses correctly in another clinical trial<sup>(37)</sup>. Immediate rises in blood phenylalanine concentrations have been described in the case of a missed dose or non-absorption of the treatment due to vomiting<sup>(24)</sup>. In principle, it might be possible to measure sapropterin concentrations to assess adherence to treatment. Given that lifelong treatment with sapropterin dihydrochloride may be given to responders to this treatment, further data on long-term efficacy and compliance are required.

#### *Fine-tuning of sapropterin dose*

The individual dose of sapropterin should be adjusted as the patient grows, within its recommended range of 5–20 mg/kg per d.

#### **Conclusions**

In PKU, the introduction of sapropterin is a welcome alternative therapy in the management of  $\text{BH}_4$ -responsive PKU. Ideally, treatment with sapropterin would lead to acceptable blood phenylalanine control without dietary treatment, but this is uncommon, and sapropterin will usually be given in combination with diet. The introduction of sapropterin raises a number of important questions relating to its optimal therapeutic use (see Fig. 1 for a summary). Long-term studies are necessary to determine nutritional adequacy, growth, body

composition, blood phenylalanine control during illness, diurnal blood phenylalanine variability, and changes in the quality and variety of foods eaten. Guidance is needed about the amount and type of natural protein that should be consumed before protein substitute is stopped and how best to introduce dietary phenylalanine with sapropterin. In addition, little is known about longer-term adherence to sapropterin treatment.

**Table 2.** Summary of the recommendations

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- There should be an international consensus on patient selection for sapropterin treatment, on the oral response test to sapropterin, on monitoring of diet and biochemical parameters, and on the financial and psychosocial impact of treatment with sapropterin and diet
  - Before starting sapropterin therapy, exact dietary phenylalanine tolerance and information about day-to-day phenylalanine tolerance should be established
  - Patients and carers should understand fully the therapeutic profile of sapropterin, the likelihood of a therapeutic response and the other possible changes to the way their disease is managed
  - Phenylalanine introduction protocols should be individually determined in responders to sapropterin, as the response to the quantity and the rate of phenylalanine introduction are variable
  - Dietary phenylalanine intake must be carefully titrated with blood phenylalanine concentrations and sapropterin dose
  - Phenylalanine-free protein substitute when used in combination with sapropterin helps to achieve micronutrient requirements, probably decreases blood phenylalanine concentrations and improves dietary phenylalanine tolerance
  - Total daily protein requirements must not be reduced below a safe level during partial or total withdrawal of the phenylalanine-free substitute
  - Careful documentation of blood phenylalanine and tyrosine concentrations, growth, nutritional status and neurocognitive function is essential at baseline and at regular intervals throughout sapropterin therapy
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Finally, managing patient and family expectations when the drug is ineffective is challenging (see Table 2 for a summary of the recommendations).

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