BIMDG
British Inherited Metabolic Disease Group

This document is intended to guide professionals in the establishment of Sapropterin-responsiveness and the monitoring of treatment in individuals with phenylketonuria who are older than 2 years of age.

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Section A: Consensus pathway for commencing Sapropterin in patients with PKU > 2 years of age

<table>
<tr><th>Activity</th><th>Information</th></tr>
<tr><td>Initial meeting

3-4 months before planning meeting</td><td>1. Ensure good blood spot sampling technique
i. Review parent/patient blood Phe spot sampling technique and provide additional training as required to ensure optimal blood spot quality. Advise that all blood spots should be taken fasting/early morning and prior to first dose of protein substitute.</td></tr>
<tr><td>Doctor / dietitian / nurse</td><td>2. Ensure maximum protein tolerance
i. For patients with most (approximately 75%) blood Phe measurements < 360µmol/L, steadily increase natural protein in 1g increments (may choose larger increment for milder phenotype).
Three – four good quality blood spot samples should be measured following each incremental increase in natural protein before increasing again. Once an increase in protein results in 2 consecutive Phe measurements > 360µmol/L (in the absence of any intercurrent illness) consider maximum tolerance to have been exceeded and reduce to last tolerated amount. Maximum safe natural protein intake is confirmed by 3 - 4 blood spots all at, or just below 360µmol/L.

ii. For patients aged > 12 years adhering to diet with most blood Phe 360 – 600 µmol/L, maximum protein tolerance (whilst maintaining Phe at their own individual target) should be established following the procedure described above.

N.B. This step should be considered part of routine clinical practice. Health professionals should have a good knowledge of natural protein intakes.</td></tr>
<tr><td></td><td>3. Regular blood Phe monitoring to establish current control
i. For patients with most blood Phe levels above target treatment range for age (Van Wegberg et al., 2017) whose aim is to improve control (i.e improving from less than 50% within range to over 75% in range), a period of regular monitoring prior to administration of sapropterin is recommended to establish variability of control. Any ongoing management with sapropterin will require blood spot Phe monitoring in line with the frequency recommended in the European Management Guidelines for routine monitoring.

Minimum frequency of blood Phe measurements (Van Wegberg et al., 2017).
<table>
<tr><th>Age (yrs)</th><th>Frequency</th></tr>
<tr><td>0-1</td><td>Weekly</td></tr>
<tr><td>1-12</td><td>Fortnightly</td></tr>
<tr><td>>12</td><td>Monthly</td></tr>
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Pre-conception	Weekly
While pregnant	Twice weekly

4. Initial discussion with parents/patient

i. Give patients and / or parents a copy of the sapropterin response testing pathway patient information leaflet

ii. Establish patient / parents / family expectations of treatment with sapropterin. Explain the long-term outcomes / expectations for ongoing prescription; these are to:

Maintain blood monitoring at the frequency required

and

Increase natural protein tolerance by 100%

or

Improve blood Phe control for those with previous poor control. (Improvement is defined as moving from less than 50% Phe measurements within target range for age to over 75% Phe measurements in range)

Target blood Phe measurements (Van Wegberg *et al*., 2017)

Age (yrs)	**Phe (µmol/L)**
0-12	120 - 360
>12	120 - < 600
Pre-conception	120 - 360
While pregnant	120 - 360

iii. Explain the need to assess responsiveness with a sapropterin response test. The definition of response being:

> 30% reduction in blood Phe from baseline

Describe what the response test entails.

iv. Explain the role of mutation analysis to exclude patients with 2 null mutations. Counsel patient/parents accordingly. Offer, and if consent is received, take a blood sample for mutation analysis.
DNA samples should be sent to Bristol Genetics lab who will undertake the single gene mutation analysis

v. Establish the need for any additional dietary education to support the response testing: calculating exchanges and weighing food (check they have electronic kitchen scales)

	Patients that are highly likely to be responsive to sapropterin (as indicated by their natural protein tolerance) can proceed to response testing without waiting for results of mutation analysis.
Results of mutation analysis	**5. Results of mutation analysis** Genetic results and their implication for responsiveness should be discussed with the patient / family. Those patients will 2 null mutations should not be considered for response testing.
Planning meeting Doctor / dietitian / nurse / pharmacist 2-3 weeks before sapropterin response test	**6. Anthropometry:** Weight, height, BMI
	7. Dietetic review i. 3-day diet diary / food frequency questionnaire (ask to complete prior to visit) ii. Calculate and document actual daily natural protein intake (exchanges) iii. Document protein substitute / protein equivalent dose
	8. Planning discussion with parents/patient i. Recap the definition of responsiveness and expectations for ongoing treatment with sapropterin ii. Advise on the frequency of blood spots required during response test iii. Ensure patient has adequate blood sampling equipment iv. Emphasise the importance of adherence with dietary management and a consistent protein intake for those patients looking to increase protein intake with sapropterin
	9. Assess readiness for pre-sapropterin baseline Phe calculation Patients consuming their maximum protein tolerance with a stable Phe at, or just below 360µmol/L (based on 4 – 6 blood spot Phe measurements from good quality blood spots taken over 4 – 6 weeks) → Proceed to calculating pre-sapropterin baseline Patients > 12 years consuming their maximum protein tolerance with Phe → Proceed to calculating pre-sapropterin baseline

	>360µmol/L and stable blood spot measurements (based on 4 – 6 blood spot Phe measurements from good quality blood spots taken over 4 – 6 weeks)	
	Patients with Phe >360µmol/L and unstable blood spot measurements (based on 4 – 6 blood spot Phe measurements from good quality blood spots taken over 4 – 6 weeks)	Advise on ensuring consistent protein / Phe intake and aiming for blood Phe stability Once blood measurements are stable within target treatment range for age proceed to calculating pre-sapropterin baseline If unable to achieve stability, assess on an individual patient basis whether to proceed to response test. Consider sapropterin response test to improve blood Phe control for those with previous poor control, section 3(i).
	Patients with Phe well below 360 µmol/L and stable blood spot measurements (based on 4 – 6 blood spot Phe measurements from good quality blood spots taken over 4 – 6 weeks)	Repeat step 2 (i) to establish maximum protein tolerance. Consider substantially increasing protein by 50 – 100% of current protein intake if a gradual increase is having little effect on blood Phe. Advise on the types of protein to use when increasing protein intake for example: cow's milk in place of low protein milk, yoghurt, shop-bought pasta instead of low protein pasta. Advise against using food that may be difficult to exclude in the future. Once Phe stable at, or just below 360µmol/L proceed to calculating pre-sapropterin baseline.
	10. Explain dose and how to administer sapropterin. i. Prescribe sapropterin at a daily dose of 20mg/kg. For children and young people under 18 years with weight > 99.6th centile the dose should be capped at a weight equivalent to 99.6th	

	centile. For those >18 years dose should be capped at a weight equivalent to a body mass index of 27kg/m^2 ii. Discuss how to administer sapropterin as per the summary of product characteristics (SPC), also discuss possible side effects of the drug. iii. Organise 28-day prescription via Blueteq.
Establish baseline blood Phe	**11. Calculate baseline blood Phe** Collect 6 early morning, fasting blood spot Phe measurements from good quality blood spots taken within 2 weeks. This can be 6 blood spots on 6 consecutive days. If blood Phe is stable, calculation of the mean of the 6 measurements forms the pre-sapropterin baseline Phe. Agree start date for commencing sapropterin response test (this needs to be as close to establishment of baseline as possible).
Response test Day 1 Dietitian / nurse	**12. First sapropterin dose** Advise to: i. Take early morning fasting blood spot sample. ii. Give sapropterin as per SPC followed by breakfast iii. Follow phenylalanine-restricted diet, consistently eating the equivalent amount of protein to that taken when establishing the pre-sapropterin baseline. (This may not be possible for those aiming to take sapropterin for improved Phe control). If you have any concerns that patients / parents may not understand how to take sapropterin correctly then video / in person observation of the first dose could be considered.
Day 2 onwards up to 28 days Dietitian	**13. Remaining days of response test** Advise to: i. Take early morning fasting blood spot sample. ii. Give sapropterin as per SPC followed by breakfast iii. Follow prescribed phenylalanine-restricted diet, consistently eating the equivalent amount of protein to that taken when establishing the pre-sapropterin baseline.

	13. Calculate response (post-sapropterin baseline) Continue regular monitoring of blood Phe measurements after starting sapropterin. The post-sapropterin baseline should be calculated from the mean of 6 (minimum) consecutive spots once a new baseline is achieved. A 30% reduction in blood Phe measurement from the pre-sapropterin baseline is considered a response to Sapropterin. Those that respond can proceed to the extension phase. Most patients are expected to respond within 48hrs. In a minority of cases a delayed response may be considered possible. A response is excluded if no response is seen within the 28-day trial period
Special considerations	**14. Illness during the first 2 weeks of response test** Pause the response test (pause taking sapropterin) until recovered from illness. If concerned, a new pre-sapropterin baseline of the mean of 6 blood spot measurements may be established, otherwise the previously established pre-Sapropterin baseline can be used. Recommence response test for up to a further 2 weeks collecting 6 early morning fasting blood spot measurements
	15. Protein intake in excess of agreed intake for duration of response test No allowances can be made for deviation from agreed protein intake during the response test.
	16. Menstruation Timing of the response test may need to take into consideration menstruation in some patients.
End of response test review. Doctor / dietitian / dietitian	**17. Discussion with parents/patient** Patients that have not responded with a 30% reduction in baseline Phe: i. Counsel patient and family to inform them that they have not responded to sapropterin ii. Advise that long term management with sapropterin is not appropriate and that they will continue with routine dietary management for PKU Patients that have responded with a 30% reduction in baseline Phe: i. Counsel patient and family to inform them that they have shown a 30% reduction in baseline Phe in response to sapropterin ii. Explain the detail of extension phase in which the patient will: • Continue their daily dose of sapropterin following the SPC

	• Take an early morning, fasting good quality blood spot each week • Progressively increase their natural protein intake in discussion with the metabolic team • Reduce their intake of Phe-free / low Phe protein substitute where possible, in discussion with the metabolic team. • Under the guidance of their metabolic doctor, reduce their sapropterin dose, where possible, in line with the SPC (a dose of 5 – 20mg/kg usually achieves and maintains blood Phe within target ranges in responsive adults and children) iii. Recap the expectations for ongoing treatment with sapropterin Increase in natural protein tolerance by 100% ***Or*** Improved blood Phe control for those with previous poor control. (Improvement is defined as moving from less than 50% Phe measurements within target range to over 75% Phe measurements in range)
	18. Dietetic review i. 3-day diet diary / food frequency questionnaire ii. Calculate and document actual daily natural protein intake (exchanges) iii. Document protein substitute / protein equivalent dose iv. Advise on increasing natural protein intake, aiming to increase protein intake by 100%
Extension Phase Up to 6 months following sapropterin response test	**19. During the extension phase** Advise to: i. Give sapropterin as per SPC followed by breakfast ii. Once per week take early morning fasting blood spot sample
Report Blood spot Phe measurements Dietitian	**20. Weekly reporting of blood spot Phe measurements** Blood Phe measurements are reported weekly and dietary adjustments made as able whilst maintaining blood Phe measurements within target range for age (Van Wegberg *et al*., 2017). Dietary adjustments may be to:

	Increase natural protein intake Review potential to increase natural protein intake in increments to enable 100% increase as soon as possible and certainly within 3 months. It is recommend that 2 blood spot samples are measured following each incremental increase in natural protein before increasing again or **Reduce protein substitute** Protein substitute will be titrated with any increase in natural protein intake (for example if natural protein is increased by 5g/day, decrease protein equivalent from protein substitute by 5g/day)
Titration of sapropterin dose Doctor	**21.** A trial of titrating to the lowest tolerated sapropterin dose should be initiated (a dose of 5 – 20mg/kg usually achieves and maintains blood Phe within target ranges in responsive adults and children)
3-month review Doctor / dietitian / nurse	**22. Anthropometry:** Weight, height, BMI
	23. Discussion with parents/patient i. Review blood spot Phe results: blood spot frequency and blood Phe control ii. Counsel if patient is unable to meet long-term outcome / expectations for ongoing prescription of sapropterin. These being to: Maintain blood monitoring at the frequency required ***and*** Increase in natural protein tolerance by 100% ***or*** Improved blood Phe control for those with previous poor control. iii. Discontinue prescription if: • patient / family does not able to meet requirements of blood monitoring • patient / family do not feel that they want to continue with Sapropterin management

	• patient is no longer responding to sapropterin on a maximum dose of 20mg/kg (can no longer tolerate 100% increase in natural protein or maintain an improvement in blood Phe measurements as previously defined), without a viable explanation.
	24. Dietetic review i. 3-day diet diary / food frequency questionnaire ii. Calculate and document actual daily natural protein intake (exchanges) iii. Document protein substitute / protein equivalent dose iv. Advise on increasing natural protein intake if potential to increase further v. Advise on reducing protein substitute as appropriate
6-month review Doctor / dietitian / nurse	**25. Anthropometry:** Weight, height, BMI
	26. Discussion with parents/patient As for 3-month review
	27. Dietetic review As for 3-month review
Ongoing follow up Doctor / dietitian / nurse	**28. Review 6-monthly**
Titration of Sapropterin dose	A trial of titrating to the lowest tolerated sapropterin dose should be initiated in all responsive patients (a dose of 5 – 20mg/kg usually achieves and maintains blood Phe within target ranges in responsive adults and children).
Outcome measures	It is proposed that the following outcome measures will be collected to guide ongoing practice in prescription of sapropterin: • Increase in protein intake • Reduction in protein substitute • Blood Phe control
Review of protocol	This protocol will be reviewed in 6 months

Section B: Pathway for women who present during pregnancy (in whom Sapropterin responsiveness is not previously known)

Immediately **start standard dietetic care for management of unplanned pregnancy, regardless of possible responsiveness to sapropterin. Do not delay standard dietetic management (including reduction of natural dietary protein intake if required).**

Doctor / dietitian	**1. Initial discussion with patient** This will need to be a highly individualised discussion with each patient, depending on clinical circumstances. Very few women are likely to fully respond to sapropterin (i.e. not requiring any additional dietary treatment) to allow them to maintain phenylalanine levels within target range for the duration of pregnancy. Prompt metabolic control during pregnancy is of critical importance. Dietary management will remain the most effective way of achieving and maintaining good metabolic control for the majority of women during pregnancy. i. Establish patient expectations of treatment with sapropterin during pregnancy. Explain the long-term outcomes / expectations for ongoing prescription and discussion of safety data on use in pregnancy ii. Explain the need to assess responsiveness with a sapropterin response test, and the potential challenges in achieving this during pregnancy due to the need to prioritise metabolic control. The definition of response during pregnancy being: > 30% reduction in blood Phe from baseline OR a clinically significant increase in natural protein tolerance (as determined by the treating team) Describe what the response test entails. iii. Explain the role of genetic mutation analysis if this has not previously been performed. Counsel patient accordingly. Offer, and if consent is received, take a blood sample for mutation analysis. DNA samples should be sent to Bristol Genetics lab who will undertake the single gene mutation analysis
Dietitian	**2. Dietetic review** Calculate and document current daily natural protein intake (exchanges) Document protein substitute / protein equivalent dose
Doctor / dietitian	**3. Explain dose and how to administer sapropterin**

	Prescribe sapropterin at a daily dose of 20mg/kg. For young people under 18 years with weight > 99.6th centile the dose should be capped at a weight equivalent to 99.6th centile. For those >18 years dose should be capped at a weight equivalent to a body mass index of 27kg/m^2 Discuss how to administer sapropterin as per the summary of product characteristics (SPC), also discuss possible side effects of the drug. Organise 28-day prescription via Blueteq.
Establish baseline blood Phe	**4. Calculate baseline blood Phe** Collect daily early morning, fasting blood spot Phe measurements from good quality blood spots starting as soon as possible once aware of pregnancy, aiming for a minimum of 2 results reflecting stable protein intake before commencing sapropterin. Standard dietetic care for management of unplanned pregnancy should continue. If blood Phe is relatively stable, calculate the mean of the most recent measurements froms the pre-sapropterin baseline Phe (minimum of 2, ideally up to 6 measurements) Agree start date for commencing sapropterin response test (this needs to be as close to establishment of baseline as possible).
Response test Day 1 Dietitian	**5. First sapropterin dose** Advise to: i. Take early morning fasting blood spot sample. ii. Give sapropterin as per SPC followed by breakfast iii. Follow phenylalanine-restricted diet, ideally eating the equivalent amount of protein to that taken when establishing the pre-sapropterin baseline (this may not be possible if dietary changes are needed to achieve or maintain Phe control)
Day 2 onwards up to 28 days Dietitian	**6. Remaining days of response test** Advise to: i. Take early morning fasting blood spot sample 2-3 times per week (depending on local protocol for maternal PKU) ii. Give sapropterin as per SPC followed by breakfast iii. Follow phenylalanine-restricted diet, ideally eating the equivalent amount of protein to that taken when establishing the pre-sapropterin baseline (this may not be possible if dietary changes are needed to achieve or maintain Phe control)

	7. Calculate response (post-sapropterin baseline) Continue regular monitoring of blood Phe measurements after starting sapropterin. The post-sapropterin baseline should be calculated from the mean of 6 (minimum) consecutive spots. A 30% reduction in blood Phe measurement from the pre-sapropterin baseline is considered a response to Sapropterin. Those that respond can continue with sapropterin for the duration of pregnancy. As in the main pathway, consideration may need to be given to special circumstances that may influence interpretation of blood Phe. Most patients are expected to respond within 48hrs. In a minority of cases a delayed response may be considered possible. A response is excluded if no response is seen within the 28-day trial period
	8. Discussion with patient i. Review blood spot Phe results: blood spot frequency and blood Phe control ii. Counsel if patient has or has not demonstrated a response to sapropterin iii. Discontinue prescription if: • patient does not feel that they want to continue with Sapropterin management • patient is not responding to sapropterin on a maximum dose of 20 mg/kg without a viable explanation
Extension Phase For the duration of pregnancy	**9. During the extension phase if sapropterin is continued** Advise to: i. Give sapropterin as per SPC followed by breakfast ii. Take early morning fasting blood spot sample 2-3 times per week (depending on local protocol for maternal PKU)
End of pregnancy	**10. Continuation of sapropterin** If the patient has demonstrated sapropterin responsiveness during pregnancy this can be continued after pregnancy and during lactation. A review to determine if the sapropterin dose could be titrated would be indicated (likely to be easier after cessation of lactation).
Titration of Sapropterin dose	The dose of sapropterin is not expected to change during pregnancy, even with pregnancy-associated weight gain

Outcome measures	It is proposed that the following outcome measures will be collected to guide ongoing practice in prescription of sapropterin: • Increase in protein intake • Reduction in protein substitute • Blood Phe control • Infant weight and head circumference measurements
Review of protocol	This protocol will be reviewed in 6 months

Van Wegberg, A.M.J., MacDonald, A., Ahring, K., Bélanger-Quintana, A., Blau, N., Bosch, A.M., Burlina, A., Campistol, J., Feillet, F., Giżewska, M. and Huijbregts, S.C., 2017. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet journal of rare diseases*, *12*(1), pp.1-56.