HSE Guideline for Sapropterin Dihydrochloride (Kuvan®) Treatment of Hyperphenylalaninaemia in Adults and Paediatric Patients with Phenylketonuria and Tetrahydrobiopterin Disorders

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

Contents

Sapropterin (Kuvan®) Guidelines

The guidelines have been reviewed by a group of prescribing physicians and healthcare professionals working in the treatment centres of excellence in Ireland. The guidelines are designed to standardise practice and support the implementation of treatment pathways for these patients in Ireland.

1.0 Introduction

Phenylketonuria (PKU) is a rare genetic disorder which prevents the breakdown of the amino acid phenylalanine (Phe) causing accumulation in the body. High levels of Phe are extremely toxic to the brain and untreated PKU causes profound brain damage resulting in very low IQ, seizures, muscle stiffness, autism, and persistent behavioural problems. In pregnancies of women with PKU, the foetus can be affected by high levels of Phe. Sapropterin (Kuvan®) treatment aims to lower the blood Phe levels to close to or below the European Guideline levels as outlined in the table below:

Patient Group	Target Blood Phe levels (µmol/L)
Patients with PKU ≤12 years	120–360
Patients with PKU > 12 years	120–600
Patients who are planning a pregnancy/are pregnant	120-360

The treatment outlined in this guideline should be initiated in an appropriate setting for the management of PKU or Tetrahydrobiopterin (BH4) Deficiency. Paediatricians will undertake to refer patients to the adult centre on reaching the age of 16-18 years. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.

Collaboration between the tertiary treatment centres and local primary and secondary care services is imperative to ensuring PKU patients receive high standards of care. Local primary and secondary care clinicians will undertake to ensure all PKU patients are referred to the specialist team in the centre for review/ input. They will endeavour to support local colleagues wherever necessary.

Prior to commencing treatment there should be a full discussion with patients/care-givers regarding the expected outcomes of therapy including the possibility of treatment discontinuation.

2.0 Patient Eligibility

To be eligible for treatment with sapropterin patients must:

- Successfully complete a three phase initiation protocol to determine short and long-term responsiveness to sapropterin.
- Meet all of the starting criteria outlined below for each phase of the protocol.

- Have confirmation of variants of the PAH gene (this confirmation is not required for neonates).

3.0 Three Phase Protocol

3.1 Phase 1: Sapropterin Loading Test

3.1.1 Starting Criteria

- A diagnosis of PKU which requires dietary treatment to keep Phe levels within age appropriate target range
- The natural protein intake is maximised prior to conducting the loading test
- Complete baseline assessments of blood Phe concentrations - 3 or more blood Phe levels must be obtained within the month prior to the start of the loading test
- Patient/carer has received appropriate counselling regarding sapropterin therapy and diet
- Discussion with patients/care-givers regarding the expected outcomes of therapy including the possibility of treatment discontinuation and signed consent

Note: In the **neonatal period** a loading test can be done before starting the diet but should not be longer than 24 hours to avoid delays in treatment.

Patients with two known sapropterin responsive mutations are not required to undergo a 48-hour loading test and are recommended to directly proceed to the Phase 2 of the protocol.

3.1.2 Exclusion Criteria

Patients who do not satisfy any of the above criteria or who meet any of the exclusionary criteria below are not considered eligible for the loading test or treatment with sapropterin.

- Patients with a diagnosis of PKU which does not require any dietary treatment including synthetic protein supplementation
- Two known null mutations in the PAH gene
- Patients with untreated Phe levels less than 360µmol/L (or 600umol/l if aged 12 or over)
- Patient/carer declines a loading test

3.1.3 Phase 1: Sapropterin Loading Test Dosing Regimen

The 48-hour loading test is carried out in an inpatient or outpatient setting (at the discretion of the physician). The loading test requires a sapropterin dose of 20mg/kg administered once daily for a total of two doses only. The second dose is administered 24 hours after the first loading dose. Blood Phe

samples are taken at 0, 8, 16 and 24 hours after **each** sapropterin administration. Correct blood sampling is crucial for a meaningful interpretation of the test.

The calculated daily dose based on body weight should always be rounded to the nearest multiple of 100mg.

3.1.4 Definition of Response to Sapropterin Loading Test

A satisfactory response is defined as a reduction in the blood Phe concentration of at least 30% from baseline

3.2 Phase 2: Sapropterin Trial

3.2.1 Starting Criteria

- Demonstrated sapropterin responsiveness as defined by 3.1.4 above
- Patient/carer agrees to send weekly blood Phe levels
- Patient/carer agrees to complete a 3-day diet record per week which is used to estimate nutrient/Phe intake and assess nutritional status

3.2.2 Phase 2: Sapropterin Trial Dosing Regimen

The purpose of phase 2 is to define the optimum dose of sapropterin required to achieve a response as defined in 3.2.3 below. Practical experience has demonstrated that assessing clinical response to a dose or diet change takes approximately 7 days and therefore reducing the twice weekly blood Phe sample requirement to once weekly will allow better control over sapropterin dose and diet.

Patients are required to submit weekly blood Phe samples during phase 2. Patients are started on a dose of sapropterin 10mg/kg/day (rounded to the nearest 100mg) initially which can be titrated weekly, to a dose between 1 to 20mg/kg/day. This should be completed within two months of initiation of phase 2.

3.2.3 Definition of Response to Sapropterin Trial

Optimum dosing of sapropterin is defined as a dose which leads to the achievement of greater than or equal to 75% of blood Phe levels within the target range of Phe less than 600 µmol/L for patients 12 years or older, and Phe less than 360 µmol/L for patients less than 12 years, and an increase in protein exchanges (at least 2-fold), with a significant decrease in synthetic protein requirement clinically appropriate to the nutritional status of the individual patient.

3.3 Phase 3: Long-Term Six Month Sapropterin Trial

3.3.1 Starting Criteria

- Demonstrated sapropterin responsiveness as defined by 3.2.3 above
- Patient/carer agrees to complete a monthly 3-day diet record which is used to estimate nutrient/Phe intake and assess nutritional status

3.3.2 Phase 3: Sapropterin Dosing Regimen

The purpose of phase 3 is to optimise the longer-term response to sapropterin treatment for the individual patient, over a six-month period. Patients are required to submit **weekly** blood Phe samples during phase 3. The dose of sapropterin can be adjusted (1-20mg/kg/day) to achieve the response as defined in 3.3.3

3.3.3 Definition of Response to Long-Term six Month Sapropterin Dosing Regimen

Long-term sapropterin responsiveness is defined as greater than or equal to 75% of blood Phe levels within the target range (Phe less than 600 µmol/L for patient 12 years of age or older, and less than 360 µmol/L for patients under 12 years of age) with an adjustment to the diet enabling an increase in protein exchanges (at least 2-fold) with a significant decrease in synthetic protein requirement clinically appropriate to the nutritional status of the individual patient.

Patients who have successfully completed the long-term six month sapropterin treatment trial and are deemed to be responders and are considered eligible for continued long-term treatment.

3.4 Special Considerations

At the discretion of the clinician, in line with international standards, sapropterin therapy may be considered for cases of maternal PKU (if women are known to be sapropterin responders and dietary treatment alone has failed), or for cases of hyperphenylalaninaemia in adults and paediatric patients of all ages with BH4 deficiency (e.g. 6-Pyruvoyl tetrahydropterin synthase (PTPS) deficiency) who have been shown to be responsive to such treatment.

4. Monitoring

4.1 Monitoring Requirements during Phase 3 Long-Term Six Month Sapropterin Treatment Trial Period

Table 3: Minimum Monitoring Requirements and Follow-Up of Patients during Phase 3

Monitoring Parameters	Frequency of Monitoring	Requirements	Monitored by
Blood Phe levels *	Weekly	≥75% must be within target range	Metabolic team
Natural protein intake	Monthly using a 3-day food diary	Increased as appropriate	Dietitian
Synthetic protein supplements	Monthly	Decreased as clinically indicated	Dietitian & clinician
Sapropterin dose review†	Monthly	Titrated to lowest dose necessary	Clinician

4.2 Monitoring Requirements during Continued Long-Term Treatment with Sapropterin

- Review the on-going prescription for sapropterin as appropriate at each clinic visit – at least 6 monthly.
- Monitor the need for vitamin and mineral supplements at each clinic visit.
- Patient/carer education to ensure strict instruction around diet, and good Phe control at each clinic visit.
- Sapropterin therapy still requires adherence to an agreed dietary regimen and regular monitoring of blood Phe levels. Blood Phe levels are monitored regularly as per age-appropriate local guidelines during the first year of long-term treatment, with a view to less frequent monitoring during subsequent years.

* If inadequate control of blood Phe levels is observed during treatment with sapropterin, patient's adherence to the prescribed treatment, and diet, should be reviewed before considering an adjustment of the dose of sapropterin[4]

† The sapropterin dose is titrated to the lowest dose necessary to maintain a response. Blood Phe levels must be maintained within the target range with sapropterin treatment and diet relaxation.[2,4,5]

5. Sapropterin Stopping Criteria

Patients will cease sapropterin treatment at any time during the 3-Phase protocol period or during continued long-term treatment if any of the following criteria apply:

- Patients are unable to tolerate sapropterin due to severe adverse events[‡]
- Diagnosis of an additional progressive life-limiting condition where treatment would not provide long term benefits
- Blood Phe levels consistently exceed the upper target range and no improvement associated with any increase in sapropterin dosage during Phase 3
- Nutritional status deteriorates as determined by the physician and dietitian
- Patients fail to attend their metabolic clinic as instructed for assessment and monitoring during the 3-Phase protocol period
- Patients on continued long-term treatment with sapropterin fail to attend their metabolic clinic twice a year for assessment and monitoring

6. Additional Information

Data Collection

Data collection will be conducted by the clinicians at the specialist metabolic centres for all patients who receive treatment with sapropterin.

Ownership of Data

By signing up to the patient-clinician contract, patients consent to having their demographic and clinical data collected by the treating clinician for clinical and administrative purposes. Information collected will include patient identifiable information (PIN) and will be stored in a manner that is compliant with General Data Protection Regulations (GDPR). Data will be shared with the HSE, the clinical team(s) for the purposes of managing patient care and assessing the benefit of treatment.

Review of Guideline and Treatment Agreement Process

This guideline will be reviewed 2 years after its initial implementation, or sooner as necessary, and adjusted if new clinically relevant data becomes available.

Audit:

[‡] Please consult the Summary of Product Characteristics for sapropterin dihydrochloride (Kuvan®) for details on adverse effects, available at www.hpra.ie

Clinical audit will be undertaken on a biannual basis. This audit will specifically review the patient cohort to ensure that clinical outcome targets (measure of efficacy) as listed in this document are reviewed and recorded.

Financial audit will be undertaken in relation to reimbursement of treatment reimbursed centrally. This will specifically monitor the claims made and compliance with eligibility criteria.

Funding of Treatment:

Patients within the public health system will be funded for their sapropterin treatment by the Health Service Executive (HSE).

Appendix 1: Membership of the Enzyme Replacement Therapy Steering Committee (September 2022)

- Interim Chair: Ms Carol Ivory, Acting Assistant National Director, Acute Operations

Representation from Paediatric Centre

- Prof Ellen Crushell, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Dr Joanne Hughes, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Prof. Ahmad Monavari, Consultant Metabolic Paediatrician, Clinical Director, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Ms Eithne Losty, Lysosomal Storage Disorders Clinical Nurse Specialist.

Representation from Adult Centre

- Prof. James O'Byrne Consultant Physician, National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin

- Ms Fionnuala King, Chief Pharmacist, AHDMP.
- Ms Rhona O'Neill, Chief II Pharmacist, AHDMP.
- Ms Nina Acosta, Senior Pharmacist, AHDMP.

Appendix 2: Document History

Version	Changes
1.0 2018	Superseded
2.0 2022	**3.1.3** The 48 hour loading test can now be carried out in an inpatient or outpatient setting as per practical experience.

	3.2.1 The Phe blood testing requirements have reduced from twice weekly to weekly based on practical experience. The turn-around time for blood tests made clinical interpretation of dose and diet adjustments difficult.
	3.2.2 The time to complete phase 2 of the protocol has been extended from one month to two months. This is based on practical experience as majority of patients starting on 10mg/kg/day will need longer than 4 weeks to reach an optimum dose.
	3.2.3 /3.3.3 The definition of clinical response to sapropterin has been amended removing the requirement for a 50% reduction in synthetic protein to "with a significant decrease in synthetic protein requirement clinically appropriate to the nutritional status of the individual patient." This is in line with European PKU Guidelines.
	3.3 Phase 3 of the protocol has been extended from 5 months to 6 months based on practical experience to optimise longer-term dose response.

References

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3. Cunningham A et al. Recommendations for the use of sapropterin in phenylketonuria. Molecular Genetics and Metabolism 2012; 106: 269-276.
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7. Van Rijn et al. Practical guidelines for the introduction of sapropterin into the management of PKU - manual for healthcare professionals. Dept. of Paediatrics, Section of Metabolic Diseases, Beatrix Children's Hospital. University Medical Centre of Groningen, The Netherlands.

8. Australasian Society for Inborn Errors of Metabolism (ASIEM). BH4 in the Management of Phenylketonuria. ASIEM Clinical Guideline Document. Accessed at https://www.hgsa.org.au/documents/item/8655 on 9/2/2018.