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Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position PP223

Sapropterin for treating hyperphenylalaninaemia (HPA) in phenylketonuria (PKU) and tetrahydrobiopterin (BH4) disorders

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PARCH - RESPECT

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Description	NHS Wales routinely commission this specialised service in accordance with the criteria described in this policy
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Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) commission sapropterin for treating hyperphenylalaninaemia (HPA) in phenylketonuria (PKU) and tetrahydrobiopterin (BH4) disorders in accordance with the criteria outlined in this document.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of sapropterin for treating hyperphenylalaninaemia (HPA) in people with phenylketonuria (PKU) and tetrahydrobiopterin (BH4) disorders who are resident in Wales. This service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 Plain language summary of PKU and BH4 disorders

Phenylketonuria is a rare, inherited metabolic disorder caused by variants in the phenylalanine hydroxylase (PAH) gene. Variants of the PAH gene result in reduced activity of the PAH enzyme, which is responsible for breaking down the amino acid phenylalanine to tyrosine. The reduced activity of PAH means that people with PKU are unable or less able to break down phenylalanine, leading to high concentrations of phenylalanine in the blood.

Tetrahydrobiopterin (BH4) deficiencies is a general term for a group of disorders characterized by abnormalities in the creation (biosynthesis) or regeneration of tetrahydrobiopterin, a naturally-occurring compound that acts as a cofactor[1]. When tetrahydrobiopterin is deficient, the chemical balance within the body is upset. In most of these disorders, there are abnormally high concentrations of the amino acid phenylalanine in the blood.

High blood concentrations of phenylalanine are toxic for the brain and can cause irreversible damage during brain development.

The treatment for PKU/BH4 is a diet to manage phenylalanine and overall protein intake (protein-restricted diet) with prescribed supplements. The diet is challenging and time-consuming, so it is difficult for some people to maintain.

In a proportion of people with PKU/BH4 disorder, sapropterin in conjunction with a protein restricted diet lowers the blood phenylalanine concentration. The aim of treatment is to maintain satisfactory blood phenylalanine concentrations to reduce PKU/BH4 disorder symptoms and complications, and potentially allow a less restricted diet.

In people under 18, treatment for PKU/BH4 disorder is particularly important because of the higher risk of irreversible brain damage to the developing brain. This risk is highest in younger children, particularly up to age 12.

[1] A cofactor is a non-protein substance in the body that enhances or is necessary for the proper function of certain enzymes.

For women with PKU/BH4 disorder who are pregnant, high phenylalanine concentrations can cause significant damage to the developing foetus. For those who respond to sapropterin, it can in conjunction with a protein restricted diet maintain the mother's phenylalanine concentration within safe levels during pregnancy.

Not all people with PKU respond to sapropterin, and the likelihood of response to sapropterin can be predicted on genetic analysis. People with two null variants are unlikely to be responsive. Most BH4 disorders are responsive to sapropterin.

1.2 Aims and Objectives

This Policy Position aims to define the commissioning position of WHSSC on the use of sapropterin for people with PKU and BH4 disorders.

The objectives of this policy are to:

- ensure commissioning for the use of sapropterin is evidence based
- ensure equitable access to sapropterin
- define criteria for people with PKU and BH4 disorders to access treatment
- improve outcomes for people with PKU and BH4 disorders.

1.3 Epidemiology

Most people with PKU/ BH4 disorders are diagnosed through newborn screening. Around 1 in 10,000 babies are diagnosed with PKU in the UK each year[2]. In Wales this equates to approximately 3 to 4 infants per year diagnosed with PKU[3]. The majority of individuals with PKU have severe variants resulting in very limited PAH gene activity. It is estimated that <30% of people with PKU in Wales are likely to respond to sapropterin.

Tetrahydrobiopterin (BH4) disorders are extremely rare affecting approximately 1:1,000,000 in the general population. Some cases, particularly mild or transient cases, may go undiagnosed or misdiagnosed, making it difficult to determine the true frequency of these disorders in the general population[4].

[2] Overview | Sapropterin for treating hyperphenylalaninaemia in phenylketonuria | Guidance | NICE
[3] Maternity and birth statistics: 2020 | GOV.WALES
[4] Tetrahydrobiopterin Deficiency - NORD (National Organization for Rare Disorders) (rarediseases.org)

1.4 Current Treatment

The primary aim of clinical management is to prevent neurological damage by keeping blood phenylalanine concentrations within the ranges recommended in the European guidelines[5].

Current clinical management of PKU is through a lifelong protein-restricted diet. This consists of prescribed low-protein and phenylalanine-free medical foods to help reduce natural phenylalanine consumption, and phenylalanine-free amino acid supplements to improve nutrition and prevent nutritional deficiencies. The protein-restricted diet also involves reducing natural protein consumption according to individual phenylalanine tolerance.

A protein-restricted diet that limits phenylalanine intake is recommended in some BH4 deficiency cases, but may not be sufficient on its own. Treatment for individuals may requires oral doses of synthetic tetrahydrobiopterin (BH4; sapropterin dihydrochloride). Individuals may also require additional therapies to counteract deficiencies such as folinic acid to prevent central nervous system folate deficiency.

People with PKU/BH4 disorder routinely undertake home dried blood spot (DBS) samples, which are then sent to a central laboratory to measure the blood phenylalanine concentrations. A healthcare professional provides the blood phenylalanine concentration results through a telephone consultation and, if necessary, will give advice on adjusting the diet to manage blood phenylalanine concentration.

Adherence and acceptance of protein-restricted diet is hindered by several factors. These include the complexity of food preparation which can be demanding and time-consuming for people with PKU, their carers and healthcare professionals who support and guide them. Patients also complain of poor palatability, disagreeable smell and textures of synthetic protein substitutes and amino acid mixtures which have to be taken in high volume (at least 3 times a day).

1.5 Proposed Treatment

Sapropterin is a synthetic version of the naturally occurring tetrahydrobiopterin. The marketing authorisation[6] for sapropterin is for adults and children of all ages with PKU who have been shown to be responsive to such treatment. Sapropterin is also indicated for the treatment of HPA in adults and children of all ages with tetrahydrobiopterin (BH4) disorder who have been shown to be responsive to such treatment.

[5] van Wegberg et al. Orphanet Journal of Rare Diseases (2017) 12:162
[6] Sapropterin dihydrochloride 100 mg Soluble Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Treatment with sapropterin should be initiated and supervised by a physician experienced in the treatment of PKU, working in a multidisciplinary team.

Response to sapropterin can either be predicted through genetic analysis or determined by therapeutic decrease in blood phenylalanine concentrations following sapropterin responsiveness challenge.

All patients may proceed to sapropterin responsiveness testing with or without genetic analysis. Patients that agree to genetic analysis should be counselled on the process, the genetic results and their implication for sapropterin responsiveness. Patients with PKU that demonstrate 2 null variants should be counselled that it is unlikely that they will respond to Sapropterin.

A stable phenylalanine concentration at baseline should be established prior to commencing Sapropterin responsiveness testing. Sapropterin responsiveness testing should be conducted in accordance with its marketing authorisation. Dietary phenylalanine intake should be maintained at a constant level during this period. A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine concentration[7]. Patients who fail to achieve this level of response within the one month test period should be considered non-responsive and treatment with sapropterin should not continue.

Once responsiveness to the sapropterin has been established, the dose may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

As HPA due to PKU/BH4 disorder is a chronic condition, once responsiveness is demonstrated, sapropterin is intended for long-term use.

Dosing information can be found in the Summary of Product Characteristics certificate[8].

1.6 What NHS Wales has decided

WHSSC has carefully reviewed the relevant guidance issued National Institute of Health and Care Excellence (NICE). We have concluded that sapropterin[9] should be made available to people with PKU and BH4 disorders that are responsive to treatment as outlined in section 2.

[7] van Wegberg et al. Orphanet Journal of Rare Diseases (2017) 12:162
[8] Sapropterin dihydrochloride 100 mg Soluble Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
[9] NICE, Technology appraisal guidance Sapropterin for treating hyperphenylalaninaemia in phenylketonuria (TA729)

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee approve funding of sapropterin as a treatment option for children and adults with PKU or BH4 disorders in accordance with the criteria identified in this policy.

2.1. Inclusion Criteria for Sapropterin for PKU and BH4 disorders

- Sapropterin is commissioned for treating individuals with:
    - hyperphenylalaninaemia that responds to sapropterin responsiveness testing as defined in the summary of product characteristics[10], in people with phenylketonuria (PKU).

    - hyperphenylalaninaemia that responds to sapropterin responsiveness testing as defined in the summary of product characteristics[11], in people with tetrahydrobiopterin (BH4) deficiency disorders.

- In treating both PKU and BH4 disorders with sapropterin, the medicinal product with the lowest acquisition cost will be prescribed in all cases. This includes patients already on treatment.

- Genetic analysis should be offered to all patients diagnosed with PKU and BH4 disorders to assess sapropterin responsiveness.

2.2. Sapropterin Responsiveness Testing

There is marked variability in dried blood spot (DBS) phenylalanine levels if bloodspot cards are used for sampling. This variability is decreased using quantitative DBS devices. For assessment of sapropterin responsiveness, it is recommended that blood samples are collected using a quantitative DBS dried blood spot (DBS) system.

A stable phenylalanine concentration at baseline should be established prior to commencing Sapropterin responsiveness testing. Once a stabilised, consistent and maximum natural protein tolerance has been established, blood phenylalanine concentrations will be recorded twice weekly for 2 weeks (total 4 samples), and the mean a phenylalanine concentration calculated.

Following commencing responsiveness testing (in accordance with its marketing authorisation), blood samples are collected twice a week (total of 8 samples) for four weeks and the mean phenylalanine concentration calculated. Throughout this period, dietary phenylalanine intake should be maintained at a constant level.

[10] https://www.medicines.org.uk/emc/product/13150
[11] https://www.medicines.org.uk/emc/product/13150

Those who exhibit ≥30% decrease in phenylalanine concentration following responsiveness testing may continue sapropterin. Sapropterin should be discontinued in those that exhibit a response of <30% decrease in phenylalanine concentration.

For those less than 16 years of age the number of protein exchanges consumed should be recorded, and a Pediatric Quality of Life inventory[12] (PedsQL) completed by child and/or parent at baseline and repeated 3 months, regardless of their responsiveness testing result

Sapropterin responders

Those who exhibit ≥30% decrease in phenylalanine concentration following responsiveness testing may continue sapropterin.

Sapropterin non-responders

Sapropterin should be discontinued in those that exhibit a response of <30% decrease in phenylalanine concentration following responsiveness testing.

Women who present during pregnancy (in whom sapropterin responsiveness is not previously known)

Women who present during pregnancy (in whom sapropterin responsiveness is not previously known) should immediately start standard dietetic care for management of unplanned pregnancy, regardless of possible responsiveness to sapropterin as prompt metabolic control during pregnancy is of critical importance. The patient should simultaneously be offered genetic variant analysis and a sapropterin responsiveness challenge.

2.3. Continuation of Treatment

After six months of treatment with sapropterin, patients can continue treatment if:

- They maintain blood monitoring at the frequency required

and

- Achieve an increase in natural protein tolerance of 100%

or

- Improved phenylanaline control in those with previous poor control (75% of phenylalanine measurements within target range)

These benefits need to be maintained to continue sapropterin treatment as assessed on a six-monthly basis. [13]

[12] https://www.pedsql.org/about_pedsql.html

[13] https://www.england.nhs.uk/wp-content/uploads/2021/12/commissioning-position-on-sapropterin-for-the-treatment-of-phenylketonuria-december-2021.pdf

Once stable, both dietary adjustments; (either increasing natural protein intake or reducing protein substitute), and a trial of decreasing the dose of sapropterin to the lowest tolerated dose can be made whilst maintaining phenylalanine concentrations within target ranges.

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating a consistent improvement to their health due to the treatment being given. If no improvement to a patient's health has been recorded then clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

Tetrahydrobiopterin (BH4) disorders

Patients with BH4 deficiency should be prescribed sapropterin in accordance with its marketing authorisation and doses should be titrated against phenylalanine concentration[9].

2.4. Stopping Criteria

If the patient does not show a ≥30% reduction in blood phenylalanine concentrations after the responsiveness testing, the patient is deemed 'not responsive' and sapropterin should be discontinued.

If the patient does not meet the six month targets as outlines in section 2.3, sapropterin should be discontinued.

Discontinuation of treatment should be done only under the supervision of a physician. More frequent monitoring may be required, as blood phenylalanine levels may increase. Dietary modification may be necessary to maintain blood phenylalanine levels within the desired therapeutic range.

2.5. Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.6. Designated Providers

Sapropterin treatment will be initiated and monitored by one of the following highly specialised providers:

Childrens service

- Birmingham Women's and Children's NHS Foundation Trust
  Birmingham Children's Hospital
  Steelhouse Ln
  Birmingham
  B4 6NH

Outreach service delivered at University Hospital Wales; Cardiff and Vale University Health Board

- Alder Hey Children's NHS foundation Trust
  Prescot Rd
  Liverpool,
  L14 5AB

Adult service:

- Cardiff and Vale University Health Board
  University Hospital of Wales
  Heath Park
  Cardiff
  CF14 4XW

- Betsi Cadwaladr University Health Board,
  Ysbyty Gwynedd,
  Penrhosgarnedd,
  Bangor
  Gwynedd
  LL57 2PW

2.7. Patient Pathway (Annex i)

See Annex i

2.8. Blueteq and reimbursement

Sapropterin for treating PKU and BH4 disorders will only be funded for patients registered via the Blueteq system and where an appropriately constructed MDT has approved its use within highly specialised centres.

Where the patient meet the criteria in this policy and the referral is received by an agreed centre, a Blueteq form should be completed for approval. For further information on accessing and completing the Blueteq form please

contact WHSSC using the following e-mail address: WHSSC.blueteq@wales.nhs.uk

If a non-contracted provider wishes to treat a patient that meets the criteria they should contact WHSSC (e-mail: TBC). They will be asked to demonstrate they have an appropriate MDT in place.

Funding is approved on the basis that sapropterin is prescribed and administered in accordance with its Marketing Authorisation[5] and that the lowest acquisition cost drug is prescribed.

In treatment is discontinued, it is the responsibility of the prescribing team to discontinue the Blueteq form.

2.9. Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.10. Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner.

These standards should include:

- Mean phenylalanine levels
- Patient reported outcome measures (PROMS)/ Quality of life
- Number of protein exchanges.

The treating centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.11. Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinician considering treatment should:

- discuss all the alternative treatment with the patient
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **National Institute of Health and Care Excellence (NICE) guidance**
  - Sapropterin for treating hyperphenylalaninaemia in phenylketonuria TA729, 22 September 2021

- **NHS England**
  - NHS Commissioning position on sapropterin for the treatment of phenylketonuria (pku) and tetrahydrobiopterin (bh4) disorders (December 2021)

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

5. Putting Things Right

5.1. Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5.2. Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

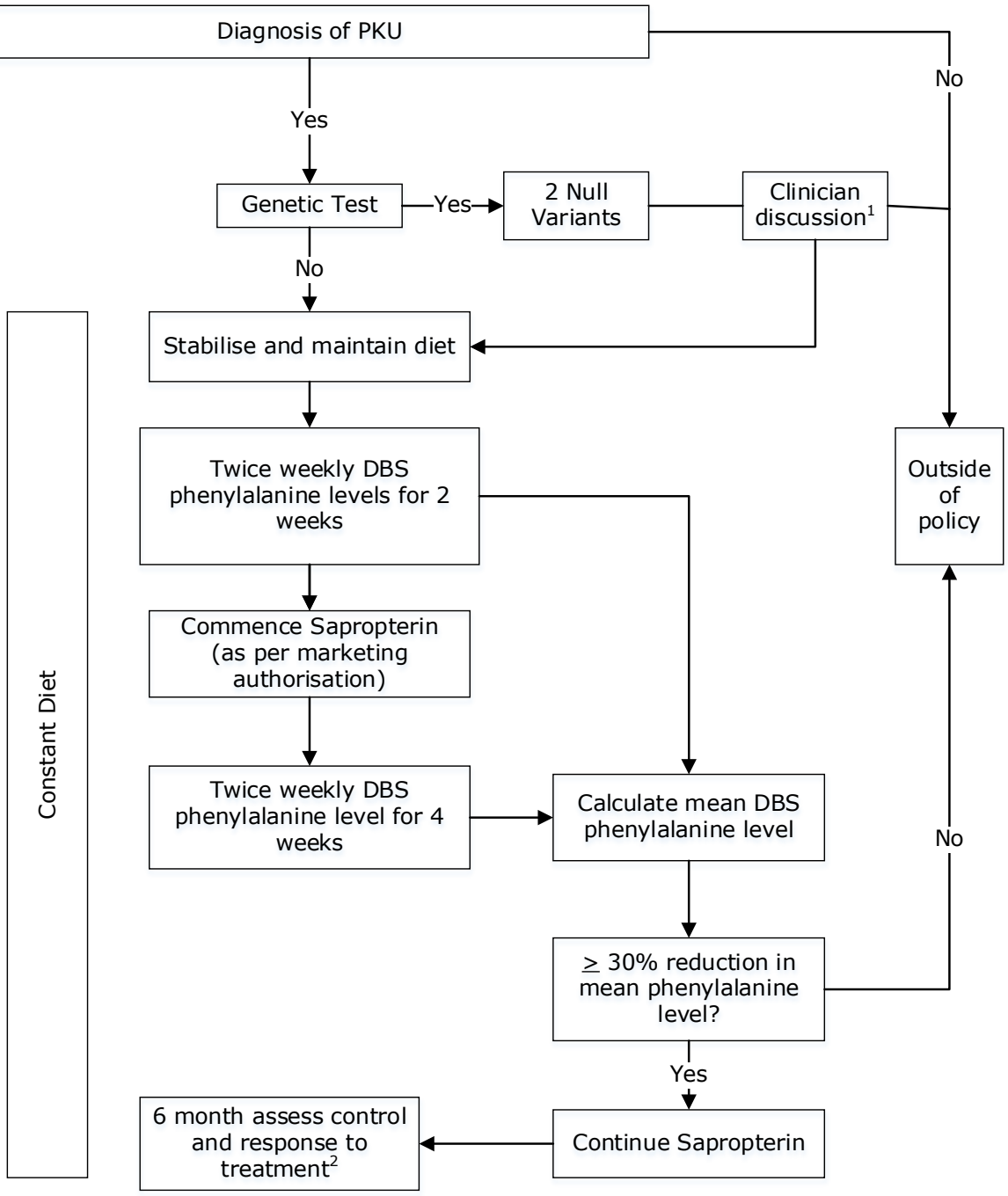
6. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

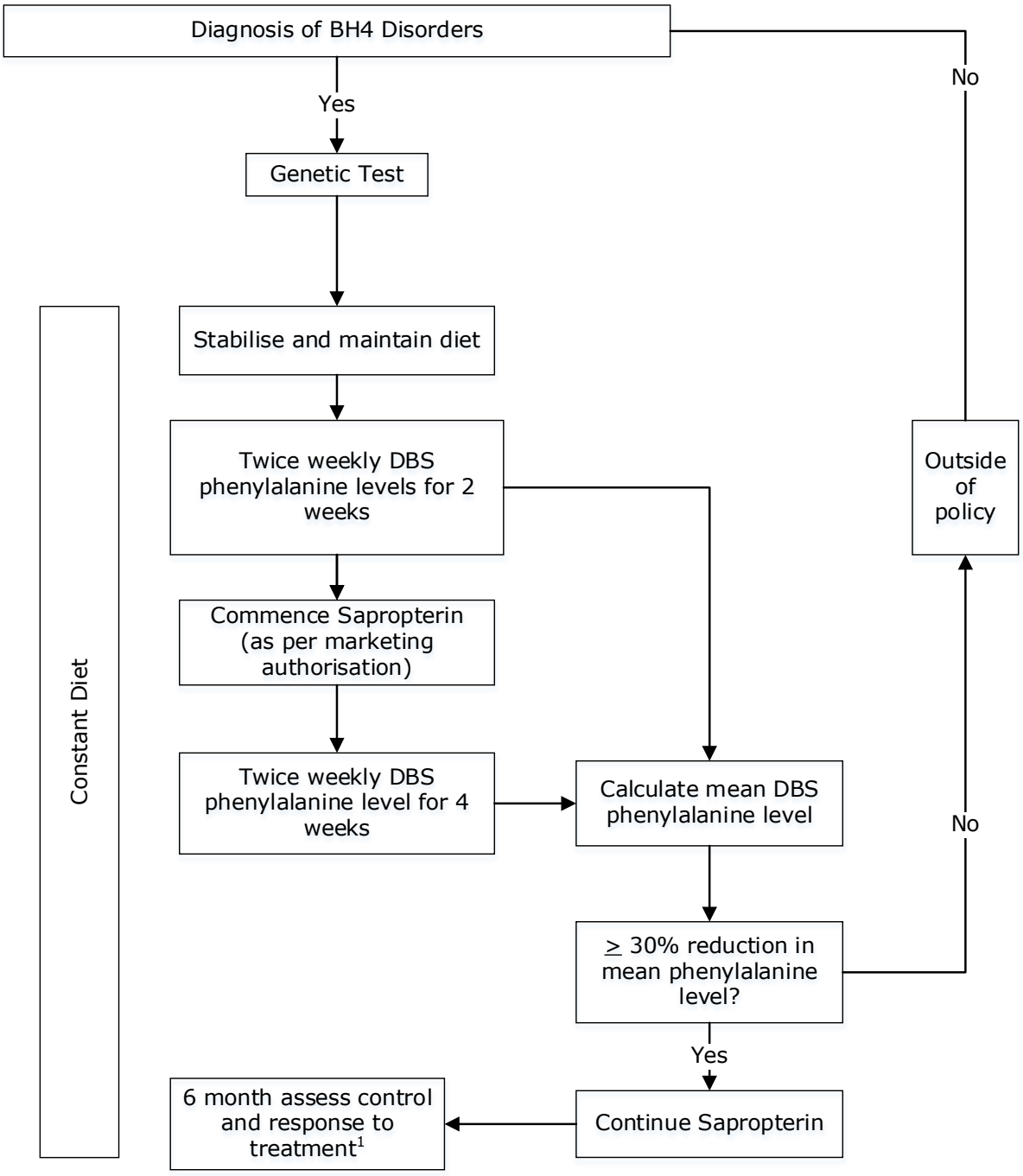
The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Patient Pathway



[1] 2 Null variants suggests that patient is unlikely to respond to sapopterin. However if the patient-clinician decide that responsiveness testing is appropriate they may proceed.

[2] See stopping criteria section 2.3



[1] See stopping criteria section 2.3

Annex ii Codes

Code Category	Code	Description
ICD-10	E70.0	Phenylketonuria
ICD-10	E70.1	Tetrahydrobiopterin (BH4) disorders

Annex iii Abbreviations and Glossary

Abbreviations

BH4 Tetrahydrobiopterin

HPA Hyperphenylalaninaemia

IPFR Individual Patient Funding Request

PKU Phenylketonuria

WHSSC Welsh Health Specialised Services

Glossary

Individual Patient Funding Request (IPFR)

An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)

WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.