NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sapropterin for treating phenylketonuria

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of sapropterin within its marketing authorisation for treating phenylketonuria.

Background

Phenylketonuria is an autosomal recessive genetic disorder caused by the deficiency of an enzyme called phenylalanine hydroxylase. Phenylalanine hydroxylase breaks down phenylalanine into tyrosine and in the absence of this, phenylalanine accumulates in the blood, resulting in brain damage. This is characterised by irreversible intellectual disability, motor deficits, skin lesions, autism, seizures, psychological, social and behavioural problems.

Phenylketonuria is typically diagnosed at birth. Since the introduction of the new born screening programmes, all babies born in the UK are routinely screened for high phenylalanine levels and neurological damage can largely be prevented by following a strict phenylalanine restricted (low protein) diet. This is a severely restrictive diet excluding all natural proteins (such as meat, fish, eggs, cheese, pulses, seeds, flour, bread and pasta).[1] Managing this diet is a substantial burden to both people with phenylketonuria and their carers and families, requiring significant knowledge, time and organisation. The diet is associated with eating disturbances and side effects such as gastrointestinal symptoms. Many people do not adhere to dietary treatment because it is very challenging and difficult to manage while living a normal life. When phenylketonuria manifests in adults it is typically characterised by a decline in executive function, depression, anxiety disorders, phobias and low self-esteem. Adults with phenylketonuria may also develop comorbidities impacting cardio-vascular and metabolic functions. It is especially important to maintain low levels of phenylalanine during pregnancy and pre-conception to avoid its harmful effects on the fetus, which can include congenital heart disease, microcephaly, developmental delay and miscarriage.

It is estimated that about 4,400 people have phenylketonuria in England.[2, 3] The rate of positive tests for phenylketonuria in babies tested in the newborn blood spot screening programme in 2016 to 2017 was 0.0137%.[4]

The mainstay of treatment in the UK is dietary protein restriction combined with dietary supplements. Sapropterin is commissioned by NHS England for pregnant women with phenylketonuria who are unable to establish adequate dietary control and achieve the target non-teratogenic range of phenylalanine (100 to 300 micromoles/L).[5]

The technology

Sapropterin dihydrochloride (Kuvan, BioMarin) is a synthetic form of BH4, a cofactor that increases the activity of phenylalanine hydroxylase, and therefore helps convert phenylalanine into tyrosine, resulting in decreased blood phenylalanine levels. It is administered orally.

Sapropterin has a marketing authorisation in the UK 'for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment'. The summary of product characteristics states that a satisfactory response is defined as a 30 percent or more reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician, within one month. The clinical trials included people with hyperphenylalaninaemia with a blood phenylalanine concentration of 400 micromoles/L or more.

Intervention(s)	Sapropterin in combination with a protein-restricted diet
Population(s)	People with phenylketonuria whose hyperphenylalaninaemia has been shown to be responsive to sapropterin therapy
Comparators	Established clinical management without sapropterin
Outcomes	The outcome measures to be considered include: • phenylalanine concentration in the blood • neuropsychological function • natural protein intake • biochemical and clinical indicators of poor nutrition • adverse effects of treatment • cognitive and mood symptoms • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of sapropterin is conditional on responsiveness to this treatment. The economic modelling should include the costs associated with establishing sapropterin responsiveness in people with phenylketonuria who would not otherwise have had a therapeutic trial.
Other considerations	If evidence allows, consideration may be given to subgroups based on: • People with childbearing potential • Age • Adherence to diet If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	None

Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for Prescribed Specialised Services 2018/19. Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domain 2. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England. Clinical Commissioning Policy: The use of Sapropterin in children with Phenylketonuria: E06/P/a NHS England. Clinical Commissioning Policy: Sapropterin (Kuvan®) For Phenylketonuria: Use in Pregnancy (April 2013) Reference: NHSCB/E12/p/a

References

1 Williams RA, Mamotte CDS and Burnett JR. Phenylketonuria: an inborn error of phenylalanine metabolism. Clinical Biochemistry Review 2008; 29(1):31-41.

2 Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2017.

3 NHS England. Clinical Commissioning Policy: The use of Sapropterin in children with Phenylketonuria. (July 2015) Reference: E06/P/a.

4 Public Health England (2017) Data Collection and Performance Analysis Report. Newborn blood spot screening in the UK 2016/17 (accessed May 2020)

5 NHS England. Clinical Commissioning Policy: Sapropterin (Kuvan®) For Phenylketonuria: Use in Pregnancy (April 2013) Reference: NHSCB/E12/p/a