NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Sapropterin for treating phenylketonuria

Draft scope (pre-invitation)

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 disorder caused by the deficiency of an enzyme called phenylalanine hydroxylase (PAH). PAH 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 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] A majority of 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 in executive function, depression, anxiety disorders, phobias and low self-esteem. Adults with phenylketonuria also 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 foetus.

There is no data on the epidemiology of phenylketonuria in adults. In 2015-16, about 4,400 people had phenylketonuria in England [2, 3] and the incidence rate of positive screening tests for phenylketonuria was 0.013% (87 babies tested positive and 672,766 babies were tested).[4]

The mainstay of treatment in the UK is dietary protein restriction combined with dietary supplements that are absent in the diet (such as nutrients and amino acids). Sapropterin is commissioned by NHS England for pregnant women.

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 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 defined hyperphenylalaninaemia as blood phenylalanine concentration≥400 µmol/L.

Intervention(s)	Sapropterin in combination with a protein diet restriction
Population(s)	People with phenylketonuria
Comparators	Established clinical management without sapropterin
Outcomes	The outcome measures to be considered include: • phenylalanine concentration in the blood • change in neuropsychological function • protein intake • nutritional biochemistry (e.g., vitamin B12) • 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.

Other 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	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf 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

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for adults with phenylketonuria?
How should established clinical management be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom sapropterin is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Will patients receiving sapropterin continue following a protein restricted diet regimen?

How is hyperphenylalaninaemia defined in clinical practice?

How is response to sapropterin treatment defined in clinical practice?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which sapropterin will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider sapropterin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of sapropterin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

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-2016.

3 NHS England. Clinical Commissioning Policy: The use of Sapropterin in children with Phenylketonuria: E06/P/a (accessed July 2018).

4 Public Health England (2017) Data Collection and Performance Analysis Report. Newborn blood spot screening in the UK 2015/16 (accessed July 2018)