NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

Givosiran for treating acute hepatic porphyria

Draft scope (pre-referral)

Draft remit/appraisal objective

To evaluate the benefits and costs of givosiran within its marketing authorisation for treating acute hepatic porphyria for national commissioning by NHS England.

Background

Acute hepatic porphyria (AHP) is a rare inherited metabolic disorder which is caused by the deficiency of one of the enzymes needed to create haem (a component of haemoglobin). Haem is formed of porphyrin, which is created from precursors including delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). In AHP, these precursors to porphyrin accumulate in the liver and other tissues. Four types of porphyria are classed as acute: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and aminolevulinate dehydratase porphyria (ADP). AIP is the most common form of AHP in the UK and has the highest symptom burden.[1]

The accumulation of precursors of porphyrin damages nerve cells and can provoke acute attacks of physical pain. AHP is life-threatening as it can lead to paralysis and respiratory arrest during acute attacks and it is debilitating in the long term because of symptoms such as pain, nausea and seizures. In addition, HCP and VP are associated with damage to the skin through sun exposure.[1] Acute attacks are very rare before puberty and usually start between 15 and 35 years old and they are more common in women.[2] There may be an increased risk of having an acute attack during or following pregnancy.[1] Most people have one or a few attacks followed by full recovery but in around 10% of cases, acute attacks are recurrent. Acute attacks are often triggered by exogenous factors such as drugs, alcohol, endocrine factors, and infection.[2]

The prevalence of AHP is estimated to be 0.1 in 10,000 people[3] in the general European population which is equivalent to around 560 patients in England.[4]

Current treatment options for people with AHP aim at eliminating or managing the symptoms and include pain management, stopping of medications that could have triggered the symptoms, gonadotrophin analogues and oral and intravenous glucose.[1,5] Haem arginate (human hemin) is indicated for the treatment of acute attacks in people with AHP. It is sometimes used outside of its marketing authorisation to prevent the attacks. Liver transplantation is an option for some people with severe recurrent acute attacks.

The technology

Givirosan (Givlaari, Alnylam) is a ribonucleic acid interference agent that suppresses the production of delta-aminolevulinic acid synthase 1 (ALAS1) by the liver in order to reduce the accumulation of the precursors of porphyrin. It is administered by subcutaneous injection.

Givirosan does not currently have a marketing authorisation in the UK for treating acute hepatic porphyria. It is being studied in a phase III placebo-controlled trial for people aged 12 years or older with a confirmed diagnosis of acute hepatic porphyria as defined by at least 2 previous acute porphyria attacks in the past 6 months.

Intervention(s)	Givirosan
Population(s)	People with acute hepatic porphyria aged 12 years or older
Comparators	Established clinical management without givorisan, which may include: • avoidance of known triggers • gonadotrophin analogues • glucose • haem arginate • liver transplantation
Outcomes	The outcome measures to be considered include: • numbers of acute attacks • porphyrin precursor concentrations in urine • neurological impairment • autonomic function • mortality • adverse effects of treatment • health-related quality of life.
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options

Clinical effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	If the evidence allows, subgroups based on the subtype of acute hepatic porphyria (that is, acute intermittent porphyria, aminolevulinate dehydratase deficiency porphyria, hereditary coproporphyria and variegate porphyria) will be considered. • guidance will only be issued in accordance with the marketing authorisation. • guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	None

Related National Policy	NHS England (2018/2019) Manual for prescribed specialised services, service 99: Severe acute porphyria service (adults and children) https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/ NHS England (2018) Highly Specialised Services Highlight report: Severe acute porphyria service (adults and children) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/12/Highly-Specialised-Services-2018-v2.pdf Department of Health and Social Care, NHS Outcomes Framework 2017-2018 (published 2016): Domains 1, 2, 3, 4 and 5. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf

Questions for consultation

Would givosiran only be used in people with recurrent acute attacks of AHP?

Would givosiran be used as a treatment for acute attacks of AHP or as a treatment for prevention of attacks in people who have had recurrent attacks?

In NHS clinical practice, would recurrent acute attacks be defined by 'at least 2 previous acute porphyria attacks in the past 6 months'?

Have all relevant comparators for givorisan been included in the scope?

Can haem arginate, glucose, gonadotrophin analogues and liver transplantation be considered as established clinical management of AHP in the NHS?

- If yes, can you define the populations likely to receive haem arginate, glucose, gonadotrophin analogues and/or liver transplant?

Does haem arginate cause any issues for any religious or cultural groups?

Are the outcomes listed appropriate?

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

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 givosiran 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 givorisan 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 givorisan 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 Evaluation 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 Highly Specialised Technology (HST) 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 British Liver Trust (2008) Porphyria. Fighting the disease. http://www.britishlivertrust.org.uk/wp-content/uploads/PPH0208_lores.pdf.pdf [accessed 26/05/20]

2 European Porphyria Network (2018) The porphyrias [accessed 26/05/20]

3 European Medicines Agency (2016) Public summary of opinion on orphan designation P https://www.ema.europa.eu/documents/orphan-designation/eu/3/16/1731-public-summary-opinion-orphan-designation-synthetic-double-stranded-sirna-oligonucleotide_en.pdf [accessed 26/05/20]

4 Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2018 [accessed 26/05/20]

5 NHS Standard Contract for Severe Acute Porphyria (2013/14) [accessed 26/05/20]