NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

Leriglitazone for andrenoleukodystrophy

Draft scope

Draft remit/evaluation objective

To evaluate the benefits and costs of leriglitazone within its marketing authorisation for treating andrenoleukodystrophy for national commissioning by NHS England.

Background

Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids (VLCFAs) results in diffuse and multifocal demyelination (when myelin is damaged) of the nervous system and adrenocortical insufficiency. In ALD, the gene (ABCD1) responsible for the breakdown of fatty acids is faulty, causing damage to the adrenal glands, myelin, brain cells and the rest of the body[1].

As the disorder is caused by a faulty gene from the X-chromosome it almost exclusively impacts upon males, as they only have one X-chromosome. Females can be affected, but the likelihood is much lower as the presence of another unaffected X-chromosome mitigates symptoms and damage. ALD can be diagnosed after blood testing for high plasma concentrations of VLCFAs and additional blood tests may be done to confirm the ABCD1 gene mutation[2,3].

ALD affects around 1 in every 17,900 males worldwide[4], or 1 in every 21,000 births[4], although estimates vary.

ALD presents with several phenotypes that differ by severity of symptoms, age of onset and gender. Those are broadly grouped as:

- Cerebral adrenoleukodystrophy (CALD) is the most common form of ALD (around 45% of cases)[5], which usually affects male children and is characterised mainly by cerebral demyelination. Symptoms tend to present between the ages of 2 and 10[6]. Progression of CALD is fast, symptoms worsen over the course of several months/years, leading to physical disability and premature death[6].

- Adrenomyeloneuropathy (AMN) is a form of ALD which affects male adults. It is characterised by neurological problems that initially mainly affects the spinal cord leading to symptoms of progressive paraparesis, bladder and bowel incontinence, impotence and adrenal insufficiency[6]. Symptoms present in the mid-20s and usually progress slowly (over many decades) but can progress rapidly (over 10 years) towards a cerebral form in 20% of males with AMN, leading to cognitive

decline, behavioral abnormalities, physical disability, or eventual premature death[7].

- Addison's disease affects male children and adults and is characterised by adrenal insufficiency. Symptom progression is slow and include extreme fatigue weight loss, darkening of skin.

Treatment of ALD varies based on the signs and symptoms in each person. For example, stem cell transplantation can be done in people with CALD (using either umbilical cord stem cells or bone marrow stem cells[6]). Steroid replacement therapy may be prescribed in people with adrenal insufficiency. Physical therapy may also be recommended to help build and maintain muscle strength.

The technology

Leriglitazone (Brand name unknown, Minoryx) is a selective peroxisome proliferator activated receptor (PPAR) gamma agonist which simultaneously activates multiple pathways and improves lipid metabolism, reduce oxidative stress, improve mitochondrial function and decrease inflammation. It is administered orally.

Leriglitazone does not currently have a marketing authorisation in the UK for treating ALD. It is being compared with placebo in a clinical trial including male adults with adrenoleukodystrophy with evidence of spinal cord involvement and without presence of brain inflammatory lesions.

Intervention	Leriglitazone
Population	Adults with adrenoleukodystrophy
Comparator	Established clinical management without leriglitazone
Outcomes	The outcome measures to be considered include: • severity of disease • motor function • neurological function • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
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	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England (2019) The NHS long term plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2 and 4. https://www.gov.uk/government/publications/nhs-

	outcomes-framework-2016-to-2017 Department of Health & Social Care (2021) The UK Rare Diseases Framework Department of Health & Social Care (2019) The UK strategy for rare diseases: 2019 update to the Implementation Plan for England Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board Department of Health (2016) The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England Department of Health (2013) The UK strategy for rare diseases National Service Frameworks Long Term Conditions (including neurological) - archived

Questions for consultation

How is ALD diagnosed in adults in clinical practice?

Is "established clinical management without leriglitazone" appropriate to describe the comparator treatments for leriglitazone?
Which treatments are considered to be established clinical practice in the NHS for adults with:

- CALD
- AMN
- Addison's disease

How long is leriglitazone expected to be given to patients?

Is the cerebral form of AMN clinically distinct from the non-cerebral from (with only spinal cord involved)? How is cerebral involvement diagnosed and treated?

Are the outcomes listed appropriate?

What is the size of the population that would be eligible for treatment with leriglitazone in England?

Are there any subgroups of people in whom leriglitazone is expected to provide greater clinical benefits or more value for money, 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 leriglitazone 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 Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology 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)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

References

1. ALEX, the leukodystrophy charity. https://www.alextlc.org/what-is-a-leukodystrophy/the-different-leukodystrophies/adrenoleukodystrophy-ald/ (accessed July 2021)

2. Great Ormond Street Hospital for Children https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/adrenoleukodystrophy (accessed July 2021)

3. ALD Connect. http://aldconnect.org/education-and-support/what-is-ald (accessed July 2021)

4. Bezman L, Moser AB, Raymond GV et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol. 2001 Apr;49(4):512-7.

5. Stop ALD Foundation. http://www.stopald.org/what-is-ald/ (accessed October 2020)

6. Engelen M, Kemp S, Visser M et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012; 7: 51.

7. HEE Genomics Education Programme. Adrenoleukodystrophy. 2019. https://www.genomicseducation.hee.nhs.uk/documents/adrenoleukodystrophy/ (accessed July 2021).