NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Leriglitazone for treating adrenoleukodystrophy

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of leriglitazone within its marketing authorisation for treating adrenoleukodystrophy.

Background

Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder which affects the nervous system and the adrenal glands. In ALD, the gene (ABCD1) responsible for a protein involved in the breakdown of very long chain fatty acids (VLCFA) is faulty. People with ALD have loss of myelin which surrounds nerves in the brain and spinal cord and damage to the adrenal glands[1].

ALD affects around 1 in every 17,000 people worldwide[2-6].

As the disorder is caused by a faulty recessive 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 and if symptoms occur this happens later in life[2]. 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[2,5].

Clinical presentation of ALD can vary greatly, with several phenotypes that differ by severity of symptoms, age of onset and gender. Those are broadly grouped as:

- Cerebral adrenoleukodystrophy (CALD), which occurs in the brain. It is the most common form of ALD (around 45% of cases)[7] and usually becomes apparent in childhood in boys. It is characterised mainly by cerebral demyelination and cognitive dysfunction. Symptoms including behavioural problems, loss of vision, epilepsy and loss of control of muscles tend to present between the ages of 2 and 10[2,6,8]. Less commonly, teenage and adult males may also develop CALD. In adults, the first symptoms are often psychiatric and can resemble depression or psychosis[2]. Progression of CALD is fast, symptoms worsen over the course of several months/years, leading to physical disability and premature death[8].

- Adrenomyeloneuropathy (AMN) is a form of ALD which affects male adults. It is characterised by neurological problems that initially mainly affect the spinal cord leading to symptoms of progressive paraparesis

(weakness or partial paralysis of the legs), bladder and bowel incontinence, impotence and adrenal insufficiency[8]. 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[6].

- Addison's disease affects male children and adults and is characterised by adrenal insufficiency without neurological features. In about 10% of ALD cases, this is the only clinical sign of the disorder[7]. Symptom progression is slow and includes extreme fatigue, weight loss and darkening of skin.

There are no treatments that stop or reverse the underlying disease process in ALD[5]. Established clinical management may include dietary changes which aim to correct the VLCFA levels, and steroid replacement therapy for people with adrenal insufficiency. Physical therapy may be recommended to help build and maintain muscle strength. Experimental treatment with stem cell transplantation may be carried out in people with CALD before physical symptoms have developed (using either umbilical cord stem cells or bone marrow stem cells)[5,8].

The technology

Leriglitazone (brand name unknown, Minoryx) does not currently have a marketing authorisation in the UK for treating ALD. It has been compared with placebo in a clinical trial including male adults with AMN with evidence of spinal cord involvement and without presence of brain inflammatory lesions. It is also being studied in paediatric and adult males with CALD.

Intervention	Leriglitazone
Population	People with adrenoleukodystrophy
Comparator	Established clinical management without leriglitazone, which may include: • steroid replacement therapy for people with adrenal insufficiency • dietary changes • physical therapy Stem cell transplant for people with CALD
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 (patient and carer-reported).
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	None
Related National Policy	NHS England (2019) The NHS long term plan NHS England (2018) NHS manual for prescribed specialist services (2018/2019) NHS England (2018) Manual for prescribed specialised services 2018/19 section 29 Haematopoietic stem cell transplantation services (adults and children), and section 119 Specialist neuroscience services for children

Questions for consultation

The condition:

What are the diagnostic criteria for ALD, CALD and AMN?

Is the paediatric form of CALD clinically distinct from the adult form?

Population:

Approximately what proportion of people in England are expected to have the ABCD1 mutation that would cause ALD?

How many new cases of ALD, CALD and AMN are seen in NHS clinical practice each year. How many people are living with ALD, CALD and AMN? What proportion of these, if any, are female?

The trials were carried out in people with AMN and CALD. Are these distinct populations? Should the clinical and cost effectiveness of leriglitazone to treat AMN and CALD be assessed separately?

Who would be eligible for treatment with leriglitazone? Would it be used to treat Addison's disease caused by ALD?

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

Treatment pathway and comparators:

Where do you consider leriglitazone will fit into the existing care pathway for adrenoleukodystrophy?

Is "established clinical management without leriglitazone" appropriate to describe the comparator treatments for leriglitazone? If so, which treatments are considered to be established clinical management in the NHS for people with:

- CALD – do these differ in children and adults?
- AMN
- Addison's disease

Are stem cell transplants considered as an option for people with ALD? If so, who would be eligible?

Outcomes and subgroups:

Are the outcomes listed appropriate? Are there other outcomes that should be listed?

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?

How long is leriglitazone expected to be given to patients?

Would leriglitazone be a candidate for managed access?

Do you consider that the use of leriglitazone can result in any potential 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 committee to take account of these benefits.

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 is 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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-tehnology-appraisal-guidance/changes-to-health-technology-evaluation).

References

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6. HEE Genomics Education Programme. Adrenoleukodystrophy. 2020. https://www.genomicseducation.hee.nhs.uk/documents/adrenoleukodystrophy/ (accessed June 2023)

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8. 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. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503704/ (accessed June 2023)