NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Leriglitazone for treating cerebral adrenoleukodystrophy in boys and men 2 years and over

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of leriglitazone within its marketing authorisation for treating cerebral adrenoleukodystrophy in boys and men 2 years and over.

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[2,3]. Estimates of birth prevalence from US newborn screening programmes range from 1 in 10,500 to 1 in 14,700[4–7].

ALD is caused by a faulty recessive gene inherited only from the X-chromosome. As a result, the disorder almost exclusively impacts males, as they only have one X-chromosome. In females, the presence of another unaffected X-chromosome mitigates symptoms and damage from ALD and if symptoms occur this happens in adulthood[2,8]. ALD can be diagnosed after blood testing for high plasma concentrations of VLCFAs, or the biomarker C26:0-lysophosphatidylcholine, and additional blood tests may be carried out to confirm the ABCD1 gene mutation[9].

Clinical presentation of ALD is variable. More than half of affected males develop the cerebral form of ALD (CALD), which usually becomes apparent in childhood[10]. It is characterised mainly by progressive loss of myelin in the brain and cognitive dysfunction. Symptoms including behavioural and cognitive problems, loss of vision, epilepsy and loss of control of muscles tend to present between the ages of 2 and 10[2,11]. Less commonly, teenagers and adults may also develop CALD. The first symptoms of CALD in adults are often psychiatric and can resemble depression or psychosis[2]. Progression is fast, symptoms worsen over the course of several months or years, leading to physical disability and premature death[9].

For people with early-stage CALD, allogenic stem cell transplantation is the gold standard and can stop CALD progressing[9]. It is available in the NHS for paediatric X-ALD with cerebral involvement and for adult male patients with early-stage CALD. Eligibility criteria for transplantation are defined as:

- a Loes brain imaging score of 9 or less and a neurological function score of 0 or 1, in boys, based on international guideline recommendations[9]

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- a Loes brain imaging score of 10 or less and an Expanded Disability Status Scale score of less than 6, in adults, based on the NHS England Clinical Commissioning Policy.

There are no other treatments that stop or reverse the underlying disease process in CALD. For people not eligible for transplant or where it would not provide benefit, established clinical management is supportive care.

The technology

Leriglitazone (Nezglyal, Minoryx Therapeutics) does not currently have a marketing authorisation in the UK for treating CALD. It has been investigated in a single-arm study in boys aged 2 to 12 with CALD before stem cell transplantation. It has also been compared with placebo in a clinical trial in men with the form of ALD called adrenomyeloneuropathy (AMN), where the occurrence and progression of cerebral lesions was investigated.

Intervention(s)	Leriglitazone
Population(s)	Boys and men 2 years and over with cerebral adrenoleukodystrophy (CALD)
Subgroups	Subgroups of CALD may include: • paediatric or adult-onset CALD • early-stage CALD who are eligible for stem cell transplantation and those not eligible for stem cell transplantation or where a transplant would not provide benefit • arrested CALD • CALD with and without gadolinium-enhancing lesions
Comparators	Established clinical management without leriglitazone, with or without stem cell transplant
Outcomes	The outcome measures to be considered for CALD include: • disease progression • neurological function, including motor and cognitive function • need for stem cell transplantation • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).

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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. NHS England (2023) Clinical Commissioning Policy: Allogeneic Haematopoietic Stem Cell Transplant for patients with X-linked cerebral adrenoleukodystrophy (Adults) NHS England (2022) UK Paediatric BMT Group HSCT Indications NHS England (2021) Clinical Commissioning Policy: Haematopoietic stem cell transplantation (HSCT) (all ages): revised reference: NHS England B04/P/a
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

Questions for consultation

Where do you consider leriglitazone will fit into the existing care pathway for CALD? Would the criteria for offering treatment differ between paediatric and adult patients?

How long is leriglitazone expected to be given to patients?

One clinical trial was carried out in boys with CALD and another was carried out in men with AMN who developed cerebral lesions. Are these distinct populations of CALD? Should the clinical and cost effectiveness of leriglitazone be assessed separately in paediatric and adult patients?

Which groups of people with CALD would not be eligible for stem cell transplant in the NHS? Are there any boys or men with CALD who would be eligible for stem cell transplant but do not have one? If yes, what are the reasons for this?

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?

Please select from the following, will leriglitazone be:

A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care

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D. Other (please give details):
For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.

How many boys and men could be eligible for leriglitazone treatment in England? How many males with CALD are under the care of NHS Inherited White Matter Disorders and Metabolic Disorders specialist services in England?

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 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.

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-technology-appraisal-guidance/changes-to-health-technology-evaluation).

References

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