NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Leriglitazone for treating cerebral adrenoleukodystrophy in people 2 years and over

Final scope

Remit/evaluation objective

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

Estimates for the prevalence of ALD vary significantly depending on the methodology and diagnostic criteria used. Newborn screening programmes from the US estimate birth prevalence of 1 in 10,500 to 1 in 14,700[1–4]. Extended family genetic screening suggests ALD affects around 1 in every 17,000 people worldwide[5,6]. Population-based studies in Europe suggest a lower point prevalence rate for ALD of 1 in 71,000 to 1 in 125,000, based on clinical presentation combined with genetic analysis.[7,8]

People with ALD have loss of myelin which surrounds nerves in the brain and spinal cord and damage to the adrenal glands[9]. Because it is caused by a faulty recessive gene inherited only from the X-chromosome, ALD 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[5,10]. 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[11].

Clinical presentation of ALD is variable, with 3 main phenotypes: cerebral ALD (CALD), adrenomyeloneuropathy and adrenal insufficiency without neurological features. These phenotypes differ in clinical course, rate of progression and impact on life expectancy. More than half of affected males develop CALD, which usually becomes apparent in childhood[12]. Symptoms including behavioural and cognitive problems, loss of vision and speech, epilepsy and loss of control of muscles tend to present between the ages of 2 and 10[5,13]. Less commonly, teenagers and adults may also develop CALD. Progression of CALD is fast, symptoms worsen over the course of several months or years. It leads to complete dependency and premature death[11]. Average survival from onset of CALD is approximately 3.5 years.

For people with early-stage CALD, allogenic stem cell transplantation is the gold standard and can stop CALD progressing. It is available in the NHS for some people with early-stage CALD. Eligibility criteria for transplantation in boys are defined as:

- a Loes brain imaging score of 9 or less and a neurological function score of 0 or 1, based on international guideline recommendations[11].

UK registry data suggest that most people with CALD do not have a stem cell transplant. This can be because they are not eligible (for example, their CALD is too advanced), there are contraindications, or no donor is available. Without a stem cell transplant, established clinical management of CALD 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.

Intervention(s)	Leriglitazone
Population(s)	People 2 years and over with cerebral adrenoleukodystrophy (CALD)
Comparators	Established clinical management without leriglitazone, with or without stem cell transplant
Outcomes	The outcome measures to be considered for CALD include: • disease progression, including major functional disability • 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).
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 (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

References

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