**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Leriglitazone for treating cerebral adrenoleukodystrophy in people 2 years and over [ID3903]
# Response to stakeholder organisation comments on the draft remit and draft scope

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comment 1: the draft remit and proposed process

| Section | Stakeholder | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | Alex, The Leukodystrophy Charity | N/a | N/a |
| | Neuraxpharm | Neuraxpharm agrees that leriglitazone (NEZGLYAL®) should be referred to NICE for appraisal, given the unmet medical need for X-linked adrenoleukodystrophy (X-ALD) within the proposed marketing authorisation (MA).<br>However, the proposed Single Technology Appraisal (STA) route is not considered suitable. Based on the evidence provided in the completed HST routing criteria, this topic meets the requirements for evaluation through the Highly Specialised Technology (HST) programme.<br>cALD is an ultra-rare, severe, and life-limiting condition with a prevalence well below the NICE threshold of 1 per 50,000. The disease is associated with rapid neurological deterioration, substantial morbidity, and early mortality. Furthermore, the eligible patient population [*redacted for confidentiality*] in | Thank you for your comments. The topic has been confirmed as a Highly Specialised Technology (HST) evaluation. |

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| | | England is estimated to be very small, approximately [*redacted for confidentiality*] (see HST checklist) which is substantially below the HST threshold of 300 patients.<br>Current clinical management options are limited and inadequate for a large proportion of patients. Haematopoietic stem cell transplantation (HSCT) is restricted to a small subset of patients and is associated with significant risks, while supportive care does not modify disease progression. There is no widely applicable pharmacological disease-modifying therapy currently available in the NHS for cALD (Engelen 2022).<br>Given the severity of the condition, very small patient population, and the lack of adequate treatment options, the technology aligns closely with NICE criteria for HST evaluation.<br>In addition, there are very few centres in the UK that are referral centres with 4 main centres commissioned under the Inherited White Matter Disorders Diagnostic and Management Service (IWMD) for all ages, three for children and one for adults. 1662-Service-Specificaton-Inherited-White-Matter-Disorders_updated.pdf | |
| Wording | Alex, The Leukodystrophy Charity | It should include that this is an oral treatment and therefore a significantly reduced burden (as compared to HSCT) as a treatment option. | Thank you for your comments. This has been added to the HST checklist. |
| | Neuraxpharm | The wording of the draft remit does not reflect the current marketing authorisation (MA). The wording should align with the clinically relevant treatment population and the available evidence base.<br>cALD is a rapidly progressive condition in which treatment effect is likely to vary depending on disease stage and eligibility for HSCT, which are key determinants of both clinical and cost effectiveness. These factors should be clearly reflected in the remit. | Thank you for your comments. The remit has been updated to remove 'men'. The updated remit considers 'people 2 years and older'. It does not capture the marketing |

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| | | In addition, given the absence of widely applicable disease-modifying pharmacological treatments and the reliance on HSCT in a limited subgroup, it would be helpful for the remit to explicitly reflect the high unmet clinical need and limitations of current management. Furthermore, the anticipated [*redacted for confidentiality*], which represents a more clinically homogeneous and decision-relevant group.<br>The following alternative wording is suggested:<br>To appraise the clinical and cost effectiveness of leriglitazone within its marketing authorisation for treating [*redacted for confidentiality*]. | authorisation (MA) wording in full because the MA is confidential and not yet final. |
| Timing issues | Alex, The Leukodystrophy Charity | Immediate urgency – this is a potentially lifesaving treatment. | Thank you for your comment. |
| | Neuraxpharm | The evaluation of leriglitazone for ccALD is of high urgency to the NHS.<br>ccALD is a rapidly progressive and life-limiting condition, particularly in paediatric patients, with neurological deterioration occurring over a short timeframe and median overall survival of approximately 3.5 years in progressive disease (Raymond et al. 2019). Delays in access to effective treatment may result in irreversible neurological damage, loss of function, and premature death.<br>Treatment options for ccALD remain limited, representing a high unmet clinical need. HSCT is only suitable for a subset of patients at an early stage of disease and is associated with significant risks.<br>For patients who are not eligible for HSCT, management is limited to supportive care, which does not modify the underlying disease progression.<br>Given the severity of the condition, the small patient population, and the absence of widely applicable disease-modifying therapies, timely evaluation and access to leriglitazone is critical. Early access could enable intervention | Thank you for your comment. No updates needed. |

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| | | before significant neurological decline, where treatment is most likely to provide meaningful benefit.<br>Therefore, this evaluation should be considered a high priority for the NHS, and efforts should be made to ensure timely appraisal and decision-making as aligned to regulatory timelines. | |
| Additional comments on the draft remit | Alex, The Leukodystrophy Charity | N/a | N/a |
| | Neuraxpharm | Overall, the draft remit needs adjusting to capture the key decision problem for evaluating leriglitazone in cerebral adrenoleukodystrophy in children (ccALD). Several points may warrant further consideration to ensure the evaluation fully reflects the clinical context and decision-making needs. | Thank you for your comments. Please see the response above about how the draft remit has been updated. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Alex, The Leukodystrophy Charity | Change “Progression is fast, symptoms worsen over the course of several months or years, leading to physical disability and premature death9” to “Progression is fast, symptoms worsen over the course of several months or years, leading to complete dependency, inability to see, speak, swallow, mobilise, cognitive decline, double incontinence and premature death.” | Thank you for your comments. The scope and HST checklist have been updated. |
| | Neuraxpharm | The background information is generally accurate and provides a clear overview of adrenoleukodystrophy (ALD) and its cerebral form (cALD), including the genetic basis, clinical presentation, and current management | Thank you for your comments. A brief description of the ALD |

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| | | options. However, several clarifications and refinements would improve completeness and ensure alignment with the decision problem.<br><br>First, while the background appropriately describes the variability of ALD, it would be helpful to more clearly distinguish between different phenotypes (e.g. adrenomyeloneuropathy (AMN) and cerebral ALD), as these have substantially different clinical courses, prognosis, and relevance to the current evaluation. In particular, the focus of this appraisal is cALD, which is characterised by rapid inflammatory demyelination and a markedly poorer prognosis compared with other forms of ALD.<br><br>Second, the description of disease burden could be strengthened by explicitly highlighting the rapid progression and poor prognosis of cALD in children (ccALD), including the short time from symptom onset to severe disability or death. This would better reflect the severity of the condition and the associated unmet clinical need as aligned to the MA and hence the population.<br><br>Third, while stem cell transplantation is appropriately identified as the current standard of care for early-stage disease, it would be useful to emphasise that this option is only suitable for a limited subgroup of patients, and that there are no widely applicable disease-modifying pharmacological treatments currently available in the NHS. This distinction is important for contextualising the role of leriglitazone.<br><br>Finally, given that the evaluation is expected to focus on the paediatric population, it may be helpful for the background section to more explicitly reflect the predominance and clinical importance of childhood-onset ccALD, which represents the most severe and rapidly progressive form of the disease. | phenotypes and how they differ has been added to the scope and the emphasis has been adjusted to focus on CALD in childhood. Also the likelihood of having a stem cell transplant has been described in more detail. |

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| Population | Alex, The Leukodystrophy Charity | Yes | Thank you for your comment. |
| | Neuraxpharm | The population defined in the draft scope is not representative to the proposed MA for leriglitazone<br><br>Specifically, while the population in the draft scope includes both boys and men with cALD, the proposed MA of leriglitazone is in [*redacted for confidentiality*].<br><br>Furthermore, treatment effect and clinical outcomes are strongly influenced by disease stage and eligibility for HSCT, which are key determinants of both clinical and cost effectiveness. These factors are particularly relevant in [*redacted for confidentiality*], where early intervention is critical. In addition, the presence or absence of, for example, gadolinium-enhancing lesions is an important marker of disease activity and may further define the most relevant treatment population.<br><br>Therefore, it may be more appropriate for the population to be defined as: [*redacted for confidentiality*] | Thank you for your comments. The population has been updated to 'people 2 years and older'. It does not capture the MA wording in full because it is confidential and not yet final. |
| Subgroups | Alex, The Leukodystrophy Charity | No, evidence suggests the outcomes of treatment are the same for eligible CALD patients regardless of age or phenotype. | Thank you for your comments. The scope has been updated to having no subgroups. |
| | Neuraxpharm | As the population is restricted to [*redacted for confidentiality*], the subgroups proposed in the draft scope are no longer relevant. | As above. |

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| | | In particular, the subgroup distinction between [*redacted for confidentiality*] should be removed, as the population is limited to [*redacted for confidentiality*].<br>Similarly, the subgroup of "arrested cALD" is not relevant, as these patients fall outside the intended treatment population.<br>Subgroups based on disease stage (early versus advanced) is also not required, as these characteristics are already inherent to the defined target population (i.e. MFD-free and HSCT-eligible patients).<br>The distinction between cALD with and without [*redacted for confidentiality*]. | |
| Comparators | Alex, The Leukodystrophy Charity | Yes - HSCT is the only comparator, however there are strict eligibility parameters and the treatment is aggressive, with several long term side effects such as infertility, increased risk of cancer, alongside complications such as Graft Versus Host Disease (GVHD). | Thank you for your comments. The suitability and side effects of stem cell transplant have been described in more detail in the scope and HST checklist. |
| | Neuraxpharm | Established clinical management without leriglitazone, including haematopoietic stem cell transplantation where appropriate. | Thank you for your comment. |
| Outcomes | Alex, The Leukodystrophy Charity | Outcomes could be more specific and include:<br>• proportion alive without major functional disabilities (MFDs)<br>• change from baseline in NfL, Loes score, lesion volume. | Thank you for your comments. MFD has been added to the scope. The outcomes listed are not exhaustive and the company is welcome |

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| | | | include additional outcomes (Nfl, Loes score or lesion volume) in its submission where relevant to the decision problem. |
| | Neuraxpharm | Given the nature of cALD and the proposed target population [*redacted for confidentiality*], it would be beneficial to ensure that outcomes explicitly capture clinically meaningful progression to severe disability. In this context, major functional disability (MFD) represents a highly relevant and patient-centred endpoint.<br><br>MFD reflects severe neurological impairment and loss of independence in one or more core functional domains (e.g. loss of communication, cortical blindness, tube feeding, wheelchair dependence, no voluntary movement and total incontinency), and is associated with substantial care needs and markedly reduced quality of life (Raymond et al. 2019).<br><br>MFD is also well aligned with established measures used in cALD, including MRI-based assessments (e.g. Loes score) and neurological function scales), and can serve as a clinically meaningful milestone in disease progression.<br><br>Including MFD as an outcome would therefore complement existing measures and help capture the most important health-related impacts of the disease.<br><br>Overall, the listed outcomes are appropriate, but could be strengthened by explicitly recognising:<br>• Disease progression as defined by major functional disability (MFD) as a key clinical endpoint, | Thank you for your comments. MFD has been added. The outcomes listed are not exhaustive and the company is welcome include additional outcomes in its submission where relevant to the decision problem. |

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| | | • neurological function, including motor and cognitive function (e.g. MRI/Loes score),<br>• patients' quality of life, and<br>• caregiver quality of life. | |
| Equality | Alex, The Leukodystrophy Charity | Leriglitazone will be a vital option for patients who are unable to find a donor match for HSCT, in particular those who are mixed race or from under-represented communities.<br>Leriglitazone will also be a vital option for patients unable to access HSCT due to physical disabilities. | Thank you for your comments. No updates needed. |
| | Neuraxpharm | Impact on families beyond patients and carers to include siblings, extended family members. | Thank you for your comments. No updates needed. |
| Other considerations | Alex, The Leukodystrophy Charity | The use of Leriglitazone to stabilise patients prior to and during HSCT is of significant benefit and should be considered. It should be noted that CALD deteriorative symptoms can continue for several months until the transplant stabilises the patient's condition.<br>The fact that Leriglitazone is an oral drug, and removes the burden of hospital stays, travel, time off etc. when compared to HSCT. | Thank you for your comments. This has been included in the HST criteria checklist. |
| | Neuraxpharm | N/a | N/a |
| Questions for consultation | Alex, The Leukodystrophy Charity | Where do you consider leriglitazone will fit into the existing care pathway for CALD?<br>Leriglitazone will be a treatment option for those diagnosed with CALD that are ineligible for or choose not to have HSCT, or to stabilise patients accessing HSCT. | Thank you for your comments. The number of boys and men with CALD has been added |

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| | | Would the criteria for offering treatment differ between paediatric and adult patients?<br>Criteria for offering leriglitazone would be similar between paediatric and adult patients<br><br>How long is leriglitazone expected to be given to patients?<br>Lifelong.<br><br>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?<br>These are expected populations of CALD but do not cover all phenotypes.<br>Clinical and cost-effectiveness – clinical effectiveness for paediatric and adult patients would follow the same assessment pathway. Cost effectiveness will be dependent on age of patient and current physical disabilities (if any). There will be a significant saving on health, social care and psychosocial costs if cerebral decline is prevented by leriglitazone.<br><br>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?<br>Boys and men with a LOES score above the cut off for HSCT.<br>Boys and men without a match donor.<br>Men with significant mobility and/or bladder problems due to AMN | to the HST checklist. No further updated needed. |

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| | | Boys and men with other unrelated disabilities or underlying conditions.<br>Boys and men who choose not to have HSCT, for example due to another family member having unsuccessful HSCT, anxiety around the aggressiveness of the treatment.<br><br>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?<br>No<br><br>Leriglitazone will be:<br>C. Prescribed in secondary care with routine follow-up in secondary care<br><br>For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.<br>No<br><br>How many boys and men could be eligible for leriglitazone treatment in England?<br><br>The Alex TLC database shows that 106 boys and men in the UK could be eligible. | |

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| | | If you take the population of England and Wales from mid-2024[1](61,806,682), incidence of 1:17,000, 50% males, 50% potential to develop CALD, at least 909 patients could be eligible.<br><br>How many males with CALD are under the care of NHS Inherited White Matter Disorders and Metabolic Disorders specialist services in England?<br>It is difficult to assess as patients are seen by either neurologists or metabolic specialists dependent on where in the UK they are. Some patients may be seen by doctors working within the IWMD Service, but not as part of an IWMD clinic.<br><br>Would leriglitazone be a candidate for managed access?<br>Yes<br><br>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?<br>Yes – in our 22 years' experience supporting patients and families affected by CALD, we know there is significant psychosocial impact to both patient and their family/carers. Challenges include ability to contribute to society for patient, parents/carers and siblings/wider family, the trauma of watching previously healthy loved ones deteriorate and die alongside caring for their increasing needs has a lasting effect with wide-reaching emotional and physical health consequences. | |

[1] https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/populationestimatesforenglandandwales/mid2024

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| | | Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.<br>• Hilary Piercy, Charlotte Nutting. The experiences of parents of children diagnosed with cerebral adrenoleukodystrophy. https://onlinelibrary.wiley.com/doi/full/10.1111%2Fcch.13184<br>• Elizabeth I Pierpont [1], Ashley R Isaia [1], Erin McCoy [1], Sarah J Brown [2], Ashish O Gupta [1], Julie B Eisengart [1.] Neurocognitive and mental health impact of adrenoleukodystrophy across the lifespan: Insights for the era of newborn screening. https://pmc.ncbi.nlm.nih.gov/articles/PMC10030096/<br>• Caroline Sevin[1], Gaëlle Thomas[2], Marieke Podevin[2]**.** Burden of cerebral adrenoleukodystrophy on affected children and their families through the eyes of family caregivers. https://www.oaepublish.com/articles/rdodj.2022.13. | |
| | Neuraxpharm | N/a | N/a |
| Additional comments on the draft scope | Alex, The Leukodystrophy Charity | Add to stakeholder list: British Inherited Metabolic Diseases Group (BIMDG) | Thank you for your comments. No updated needed – the BIMDG is already included. |
| | Neuraxpharm | N/a | N/a |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

NPPG (Neonatal and Paediatric Pharmacy Group