**National Institute for Health and Care Excellence**

**Single Technology Appraisal**

**Idebenone for treating visual impairment in Leber's hereditary optic neuropathy [ID547]**

**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 | Chiesi Farmaceutici S.p.A | Chiesi agrees that it is appropriate to refer this topic to NICE for appraisal. However, the proposed referral to the Single Technology Appraisal (STA) is not suitable for idebenone and it should instead be referred to NICE's Highly Specialised Technology (HST) programme as this is a treatment for an ultra-rare condition.<br><br>The number of prevalent patients who are symptomatic with visual loss with Leber's hereditary optic neuropathy (LHON) and potentially appropriate for treatment is **substantially lower than the figures in the draft scope** for the symptomatic population carrying the mutation and is estimated to be ~ **293** people in England.<br><br>Further information is provided below regarding how idebenone meets the HST programme eligibility criteria. | The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a single technology appraisal. Please see the final HST checklist for details. |

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| | GenSight Biologics SA | The proposed evaluation route of a single technology appraisal (STA) is appropriate for idebenone. We would not consider idebenone a highly specialised therapy. | |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | We welcome this appraisal as an opportunity to evaluate Idebenone. We note that Idebenone is available to people living with Leber's Hereditary Optic Neuropathy (LHON) in Scotland and Wales, this naturally leads to significant inequity in the chance of any sight recovery for people in England compared to the rest of the residents in the United Kingdom.<br><br>We would, however question the rationale of this being a Single Technology Appraisal given that Lenadogene nolparvovec was selected for the Highly Specialised Technology Appraisal. In the previous acknowledgement that the disease meets the criteria for HST we would comment that:<br>1. The disease is very rare<br>2. The population eligible for Idebenone is small<br>3. This very rare disease results in significant affects on the quality of life for those living with LHON<br>There are no other satisfactory treatment options (unless you live in Scotland or Wales) | The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a single technology appraisal. Please see the final HST checklist for details. |
| | The Lily Foundation | We are unclear why the proposed evaluation route for Idebenone is for single technology appraisal rather than highly specialised technology evaluation.<br><br>Last year we were asked to comment on the scope for another product to treat LHON (Lenadogene nolparvovec, ID1410), and this was originally proposed to be evaluated through the highly specialised technology evaluation route. We would like to better understand the rationale behind this change, as we feel that if Lenadogene was intended to be proposed for HST appraisal then Idebenone should be assessed in the same way. | The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a single technology appraisal. Please see |

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| | | We acknowledge that LHON doesn't exactly fit the HST criteria in terms of prevalence, (affecting an estimated 2,072 people in England based on 2018 stats), we believe that Idebenone very strongly and clearly satisfies the final 2 criteria for the HST route. LHON severely impacts quality of life, with a rapid onset causing severe sight impairment within a matter of months. This is devastating in terms of quality of life for those who are affected, especially because LHON most commonly occurs in teenagers and those up until their 30s who have their whole lives ahead of them.<br><br>In addition, there are currently no satisfactory treatment options for patients with current management being based on supportive care. | the final HST checklist for details. |
| | Genetic Alliance UK | No comments | No action required |
| Wording | Chiesi Farmaceutici S.p.A | Chiesi agrees that the wording reflects the issues of clinical and cost-effectiveness of this technology. | No action required |
| | GenSight Biologics SA | Yes | No action required |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | The wording is reflective | No action required |
| | The Lily Foundation | The scope doesn't appear to go into great detail about the cost of Idebenone versus the ongoing economic impact of supportive care and management to the NHS. | No action required |

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| | | For patients living with LHON, any improvement to their symptoms has the potential to be life-changing, allowing people to lead more independent lives, contribute to society and be less reliant on health and social care systems; all of which have a significant economic impact and should be taken into account when considering the cost effectiveness of treatment. | |
| | Genetic Alliance UK | No comments | No action required |
| Timing issues | Chiesi Farmaceutici S.p.A | There is a relative urgency of this evaluation to the NHS given that there are currently no other licensed treatments recommended for patients with LHON in England and no new treatments are currently expected to be recommended. A timely evaluation will ensure that eligible patients with high unmet need will have access to idebenone at the earliest opportunity.<br>LHON is a very rare maternally inherited neurodegenerative mitochondrial disease causing progressive loss of vision in young adults.<br>Only a proportion of the total population carrying the LHON mutation (estimated as 10% of females and 50% of males) will develop vision loss. These patients suffer from sudden and rapid bilateral vision loss, which is irreversible in most patients following degeneration of retinal ganglion cells (RGCs) in the late, chronic stage of the disease.[1,2]<br>There are currently no specific guidelines available for the management of LHON and there is a need for effective treatment strategies. Current clinical practice is limited to standard of care (SoC) which consists of lifestyle management, genetic counselling and supportive treatments.[3]<br>Idebenone is the first and only licensed treatment for LHON and has already been granted national reimbursement in Wales and Scotland. [4–6]<br>There is, therefore, a high unmet need for patients with LHON in England to have timely access to an effective disease-specific treatment which aims to | Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: Project information \| Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over ID547 \| Guidance \| NICE |

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| | | prevent further vision loss and promote recovery of lost vision, in line with patients in other parts of the UK. | |
| | GenSight Biologics SA | None | No action required |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | People living with LHON in England should have access to sight saving or sight improving treatment and so, this is evaluation is extremely urgent. We would urge NHS England and NICE to remind payers and prescribers that the absence of NICE guidance should NOT prevent access to medicines should there be clinical need. Essentially, no patient should lose their sight because this topic has not been evaluated previously. | Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: Project information \| Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over ID547 \| Guidance \| NICE |
| | The Lily Foundation | We see this evaluation as extremely urgent. Early intervention is crucial with LHON as natural history suggests loss of vision spreads rapidly to the second eye after onset, and severe visual loss can happen within a matter of months.<br>This is devastating at any age but is especially cruel for teenagers which is the most common age of onset. | Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: Project information \| Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 |

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| | | | years and over ID547 \| Guidance \| NICE |
| | Genetic Alliance UK | No comments | No action required |
| Additional comments | Chiesi Farmaceutici S.p.A | As outlined above, Chiesi has considerable concerns regarding the proposed referral of idebenone to the STA programme and urge NICE to reconsider this recommendation.<br><br>To aid this decision, Chiesi has provided an overview of eligibility based on the four eligibility criteria for the HST programme.<br><br>**1. The disease is very rare**<br>The prevalence of LHON in people aged 12 years or over is approximately **975** patients in England with <**300** patients affected by sight loss:<br>• LHON is an ultra-rare, maternally inherited neurodegenerative mitochondrial disease causing progressive loss of vision in young adults. The exact number of people affected by LHON is still unknown, however, it is estimated that the prevalence of people carrying LHON mutations is approximately 1 in 50,000.[7] This equates to an approximate prevalence of **975** people in England based on the predicted population of England aged 12 years or over in 2021 of 48,743,750.[8,9]<br>• Crucially, an unknown environmental trigger is needed to develop symptoms of LHON and many affected patients of LHON never suffer visual loss. The incidence of visual loss, therefore, is likely to be much less than the prevalent figure of 1 in 50,000. It is estimated that only 10% of females and 50% of males with an underlying LHON mutation will experience visual impairment.[7] Considering this, the number of | The routing of this topic was discussed in the topic selection oversight panel meeting and it was considered that this topic would be routed as a single technology appraisal. Please see the final HST checklist for details. |

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| | | prevalent patients who are symptomatic with visual loss is substantially reduced compared to the overall prevalence figures described above.<br>• It is estimated there are <300 people in England affected by visual loss based on the above assumptions and a 50:50 gender split with the mutation.<br><br>**2. Normally, no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indication**<br><br>• As based on the assumptions above, the group of patients carrying the LHON mutation and affected by sight loss is estimated at 293 patients.<br><br>**3. The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life**<br>• Vision loss due to LHON has a major impact on patient wellbeing and affects almost all aspects of life, such as activities of daily living, emotional functioning, relationships, studies, work and recreation, exacerbated by the young age of symptom onset.[10] This causes a substantial decrease in patient quality-of-life (QoL).<br>• Patients' QoL is further impacted as patients often struggle to cope with the vision loss in the weeks and months following their often-long-awaited diagnosis, as they are unable to carry out the everyday activities they were once used to doing.<br>• Visual impairment in LHON is associated with significantly negative psychological and psychosocial effects in adolescents, young adults and middle-aged adults. Vision loss due to LHON can have a negative impact on interpersonal relationships and career goals.[11] | |

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| | | • Furthermore, LHON generates a significant burden for caregivers and substantially impacts caregivers' lives, emotional functioning, and work, causing a substantial impact to the QoL of carers. Caregivers are often family members and become highly involved in the LHON patient's life, often having to fit their own lives around caring for a patient with LHON. The burden of caregiving can also impact their work since many carers have to stop working or reduce their working hours.[10]<br>• Family members caring for patients with LHON often have to dedicate more vigilance, time and efforts to the patient's activities of daily living such as dressing, meals, shopping and transport often resulting in increased mental and physical exhaustion of the caregiver.[10,12]<br><br>**4. There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options**<br>• There are no other approved therapies for LHON in the UK. Idebenone is the first and only licensed disease-specific treatment for visual impairment in adolescents and adults with LHON. Current treatment of patients with LHON in England does not target the underlying neurodegenerative condition and is limited to non-pharmaceutical SoC which comprises an extensive list involving lifestyle management (avoiding tobacco, alcohol, exposure to drugs and toxins with mitochondrial toxicity), genetic counselling and supportive treatments. The benefit of such treatment approaches in LHON patients remains limited and variable.[13]<br>• Idebenone is the first and only disease-specific treatment for visual impairment in adolescents and adults with LHON and has demonstrated the potential to re-activate viable-but-inactive RGCs | |

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| | | in LHON patients across the three primary mutations (m.11778G>A, m.14484T>C and m.3460G>A).[4] Idebenone was granted an 'orphan medicine' status on 15th February 2007.[4]<br><br>Chiesi believes that idebenone therefore fulfils all of the HST programme criteria and should be considered for HST routing.<br><br>Furthermore, Chiesi agreed with the draft scoping for lenadogene nolparvovec (now suspended) that proposed the therapy was routed for assessment via the HST programme. Although Chiesi strongly do not agree that lenadogene nolparvovec is a relevant comparator, for reasons highlighted in the 'Comparators' section of the draft scope, both medicines should be assessed using the same NICE process and methodology. Otherwise, an inequity between patients with LHON and their chances of accessing an effective treatment will have developed. | |
| | GenSight Biologics SA | Please note that idebenone was granted marketing authorisation on 08/09/2015. This means as an orphan drug, they have market exclusivity until 2025. NICE should consider if it is appropriate to appraise a product when generic versions could be available from 2025. | Comment noted. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | No comments | |
| | The Lily Foundation | No comments | No action required |

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| | Genetic Alliance UK | No comments | No action required |

**Comment 2: the draft scope**

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| Background information | Chiesi Farmaceutici S.p.A | Chiesi would like to note that the prevalence figures of LHON provided in the draft scope of 3.22 or 3.65 per 100,000, and the estimated total eligible population in England of 2,072 people are not accurate. These figures are estimated from the prevalence of LHON cases in the North-East of England, which is a relatively small sample and may not be generalisable to the whole English population. Furthermore, the unusual methodology used to estimate prevalence in the study likely overestimates the figures. As detailed above, Chiesi considers it more robust to use the worldwide prevalence as an estimate. Worldwide, the prevalence of LHON is estimated to be 1 in 50,000 people.[7] Applying this rate to the estimated 2021 English population aged 12 years or over of 48,743,750 results in an estimated **975** patients with LHON.[8,9]<br><br>Furthermore, a key point is that a proportion of the total population carrying the mutation will never suffer visual loss; it is estimated that only 10% of females and 50% of males with an underlying LHON mutation will experience visual impairment.[1]<br><br>The number of prevalent patients who are symptomatic with visual loss and potentially appropriate for treatment is therefore likely to be **substantially lower than the figures in the draft scope** for the symptomatic population carrying the mutation and is estimated to be **~ 293** people in England, based on the above assumptions and a 50:50 gender split for the mutation. | NICE considers that the figures given in the draft scope for UK prevalence are the most robust and relevant available for this condition |

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| | GenSight Biologics SA | Please add a comment that idebenone is for the treatment of all LHON mutations. | Comment noted. Idebenone will be appraised within its marketing authorisation. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | Broadly the background is accurate however the total number of people affected would appear to be an over estimate. | NICE considers that the figures given in the draft scope for UK prevalence are the most robust and relevant available for this condition |
| | The Lily Foundation | Accurate | No action required |
| | Genetic Alliance UK | No comments | No action required |
| Population | Chiesi Farmaceutici S.p.A | Chiesi agrees that the population proposed in the scope is defined appropriately, as this aligns with the population included in the European Marketing Authorisation (EMA) marketing authorisation. | No action required |
| | GenSight Biologics SA | Yes | No action required |

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| | Leber's Hereditary Optic Neuropathy (LHON) Society | Yes | No action required |
| | The Lily Foundation | Accurate | No action required |
| | Genetic Alliance UK | No comments | No action required |
| Subgroups | Chiesi Farmaceutici S.p.A | Chiesi agrees that the subgroup suggested in the scope is appropriate to consider.<br>The inclusion of the subgroup of patients with recent vision loss (acute LHON) will be given due consideration, subject to available evidence. | No action required |
| | GenSight Biologics SA | Patients treated between 0 to 6 months from the onset of symptoms (sub-acute phase), 6- 12 months from the onset of symptoms (dynamic phase), more than 12 months from the onset of symptoms (chronic phase).<br><br>Adolescent patients between the ages of ≥12 to 15 and patients over 15 years of age.<br><br>Chain complex 1 genes, mitochondrial genes ND1, ND4 and ND6. | Comments noted. If evidence allows, other subgroups not listed in the scope should be presented in the evidence submissions for the committee to consider. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | We would question the requirement to assess sub populations. | Comment noted. No action required. |

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| | The Lily Foundation | No | No action required |
| | Genetic Alliance UK | No comments | No action required |
| Comparators | Chiesi Farmaceutici S.p.A | Chiesi agrees with the proposed comparator of "established clinical management without idebenone" as there are currently no licensed disease-modifying treatments available for patients with LHON in England.<br><br>Chiesi strongly does not agree with the proposed comparator of lenadogene nolparvovec within this evaluation due to the following reasons:<br><br>• Lenadogene nolparvovec does not have a marketing authorisation for treating loss of vision due to LHON. The application for authorisation of lenadogene nolparvovec was withdrawn from the EMA on 20th April 2023[14] and the planned NICE appraisal (via the HST programme) suspended on 6th June 2023.<br>• There is currently no established clinical practice for the treatment of LHON in the NHS and idebenone is the first and only licensed treatment available for patients with LHON.<br>• Lenadogene nolparvovec was targeted only to patients with LHON who have the m.11778G<A mutation. Idebenone is not restricted to a particular mutation and has demonstrated efficacy in all major mutations associated with vision loss due to LHON. In the LEROS study, clinically relevant response (CRR) was observed in nearly 90% of eyes with the T14484C mutation, 47% of eyes with the G11778A mutation, and 43.7% of eyes with the G3460A mutation.[15] | Comment noted. Because the NICE appraisal of lenadogene nolparvovec has been suspended, it is not expected to be established clinical practice at the time of appraising idebenone. Therefore lenadogene nolparvovec has been removed as a comparator from the scope. |

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| | | Therefore, Chiesi do not consider lenadogene nolparvovec an appropriate comparator as it does not have a marketing authorisation or planned NICE evaluation, it is not part of established clinical practice in England and it is only targeted to patients with one particular mutation. For these reasons, it should be removed from the scope of this appraisal. | |
| | GenSight Biologics SA | Yes | No action required |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | Lenadogene nolparvovec is an unlicensed, research stage product and should not be considered a comparator | Comment noted. Because the NICE appraisal of lenadogene nolparvovec has been suspended, it is not expected to be established clinical practice at the time of appraising idebenone. Therefore lenadogene nolparvovec has been removed as a comparator from the scope. |
| | The Lily Foundation | As Lenadogene currently remains an unlicensed product (thus unavailable to patients in the UK outside of a clinical trial), we are unclear if this can be considered a comparator. | Comment noted. Because the NICE appraisal of lenadogene nolparvovec has been suspended, it is not |

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| | | If not, we believe that the best current comparator to Idebenone is supportive care; including monitoring, psychological and social support and the use of visual aids.<br><br>However, if Lenadogene was to be licensed in the future, we believe that together the two products could form the first treatment pathway for patients affected by LHON in the UK and offer a real alternative to the standard supportive care offered by the NHS. | expected to be established clinical practice at the time of appraising idebenone. Therefore lenadogene nolparvovec has been removed as a comparator from the scope. |
| | Genetic Alliance UK | One of the comparators stated in the draft scope is Lenadogene nolparvovec. As it is subject to a NICE evaluation, it is therefore not widely available and as far as we understand, the definition of a comparator is a technology that is routinely used in the NHS, therefore we have concerns that this comparator appears to be outside of the usual definition of a comparator.<br><br>We understand that there may be circumstances that are appropriate to use technologies that are currently being assessed by NICE as a comparator but we would appreciate an overview of how decisions about expanding the definition of a comparator are made, and a discussion with the patient community as to the potential risks and benefits of using comparators outside of the definition and when it may be appropriate to do so. Otherwise, we fear this may lead to an inconsistency and inequality between appraisals. | Comment noted. Because the NICE appraisal of lenadogene nolparvovec has been suspended, it is not expected to be established clinical practice at the time of appraising idebenone. Therefore lenadogene nolparvovec has been removed as a comparator from the scope. |
| Outcomes | Chiesi Farmaceutici S.p.A | Chiesi appreciates that the proposed outcomes capture important health related benefits for patients with LHON.<br><br>However, Chiesi has concerns that the proposed outcome measures of macular thickness and immune response do not align with the data that is | Outcomes amended as suggested. |

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| | | available from the RHODOS study. RHODOS was a randomised, double blind, placebo-controlled study assessing whether administration of idebenone can improve visual function in LHON patients.<br><br>Macular thickness and immune response were not endpoints collected in the RHODOS trial. Therefore, Chiesi would suggest that NICE reconsiders the inclusion of these measures and remove them from the scope of this appraisal. | |
| | GenSight Biologics SA | Include time to clinical improvement. | Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | The outcomes would seem appropriate | No action required |
| | The Lily Foundation | Accurate. As a patient organisation we would like to draw particular attention to the importance of health-related quality of life as one of the listed outcomes. We have heard anecdotal evidence from our patient population that treatment with Idebenone has transformed their quality of life, allowing them the ability to regain some independence and vastly improve their quality of life. | Comment noted. No action required |
| | Genetic Alliance UK | No comments | No action required |

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| Equality | Chiesi Farmaceutici S.p.A | No equality issues have been identified. | No action required |
| | GenSight Biologics SA | No change required. | No action required |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | We welcome this appraisal and acknowledge it's importance in ensuring equality for people with various states of vision loss due to LHON.<br><br>As previously stated, under current circumstances inequalities exist for citizens of the United Kingdom affected by LHON, so called "postcode prescribing" exists whereby an individual has significant changes of sight recovery or protection based upon where they live in the United Kingdom. Essentially a resident of Northumbria is left to lose their sight, whereas a resident of Galashiels would access active treatment to protect or restore vision loss. This is an absurd inequlity. | Comment noted. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. |
| | The Lily Foundation | We believe that there is currently a huge discrepancy in terms of equality of access to Idebenone throughout the UK. Idebenone has a marketing authorisation in the UK for LHON, and yet it is not currently commissioned for routine use in the NHS in England.<br><br>We feel that this is unfair, given that patients living in Scotland and Wales are able to receive Idebenone but those living in England cannot. In essence, this creates a 'postcode lottery' for patients living in the UK and discriminates against those who are currently resident in England who are unable to access a treatment for the same condition. | Comment noted. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. |

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| | Genetic Alliance UK | No comments | No action required |
| Economic analysis | Chiesi Farmaceutici S.p.A | Chiesi is broadly aligned with the overview of the economic analysis outlined in the draft scope. However, Chiesi proposes that the sentence: “the cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye” should be changed to “the cost effectiveness analysis should include consideration of the benefit in the best seeing eye”.<br>LogMAR VA is measured in the better-seeing eye rather than the worst-seeing eye. This is because Brown et al. (1999) demonstrated that a patient’s quality of life is attributed more by the better-seeing eye than the worst-seeing eye.16 In addition, the better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye. | This sentence is standard wording in NICE scopes for all appraisals in eye conditions. No action required. |
| | GenSight Biologics SA | No comments | No action required |
| | Leber’s Hereditary Optic Neuropathy (LHON) Society | No comments | No action required |
| | The Lily Foundation | No comments | No action required |
| | Genetic Alliance UK | No comments | No action required |

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| Other considerations | Chiesi Farmaceutici S.p.A | Idebenone is an innovative therapy which addresses a severe unmet need by providing the first efficacious treatment option for patients with visual impairment due to LHON. If approved, idebenone would represent a step change in the management of vision loss for patients with LHON. The rapid and persistent lifelong severe visual impairment that occurs in patients with LHON represents a substantial humanistic and economic burden for patients and carers. Current supportive treatments for these patients do not have any substantial benefit in alleviating the burden of the disease and negligible benefit in slowing progression of the disease. The clinical efficacy demonstrated by idebenone in preventing vision loss and allowing recovery of visual function therefore represents a shift in the treatment paradigm for patients who would otherwise not receive efficacious treatment. The severe unmet need of these patients should be considered during the appraisal. | Comment noted. No action required. |
| | GenSight Biologics SA | The impact of LHON on the Carer and wider family burden should also be included in the evaluation. | Comment noted. The evaluation will consider all relevant health effects including carers if relevant. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | None | No action required |
| | The Lily Foundation | None | No action required |

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| | Genetic Alliance UK | No comments | No action required |
| Questions for consultation | Chiesi Farmaceutici S.p.A | **Where do you consider idebenone will fit into the existing care pathway for LHON?**<br>Idebenone will be the first licensed treatment, given that no other pharmacological treatment options are available.<br>**Have all relevant comparators for idebenone been included in the scope? Which treatments are considered to be established clinical practice in the NHS for LHON in England?**<br>The only comparator that is relevant to include in the scope is 'established clinical management without idebenone'. As detailed above, lenadogene nolparvovec is not established clinical practice in England, does not have a marketing authorisation for treating loss of vision due to LHON and, as of 6th June 2023, the NICE evaluation for lenadogene nolparvovec has been suspended. Furthermore, lenadogene nolparvovec is also not intended to be used in the same population as idebenone, because it targets only LHON caused by the m.11778G<A mitochondrial DNA mutation, whereas idebenone has demonstrated efficacy in several LHON-associated mutations.<br>Therefore, lenadogene nolparvovec should not be included as a comparator in this scope and only 'established clinical management without idebenone' should be considered as a relevant comparator for this appraisal.<br>**Are the outcomes listed appropriate? Should outcomes related to the non-vision related symptoms of LHON be included?**<br>The outcomes listed in the draft scope should align to the clinical endpoints reported in the RHODOS trial which are considered most relevant to vision- | Lenadogene nolparvovec removed from scope. Comparator will be established clinical management without idebenone only.<br>Outcomes amended as suggested |

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| | | related symptoms of LHON. Outcomes considered in the scope should therefore include:<br>• visual acuity<br>• contrast sensitivity<br>• retinal nerve fibre layer<br>• visual field assessment<br>• adverse effects of treatment<br>• health-related quality of life<br>Outcomes related to non-vision related symptoms of LHON are also relevant to consider as part of the submission, such as cardiac conduction defects, neurological abnormalities, and skeletal abnormalities, which are sometimes reported in LHON patients.[1] While data on these outcomes are not collected as part of the clinical trials and therefore should not be included in the final scope, the effects of idebenone on non-vision features of LHON may be considered qualitatively outside of the QALY calculation.<br>**Are there any subgroups of people in whom idebenone is expected to be more clinically effective and cost effective or other groups that should be examined separately?**<br>Idebenone has demonstrated clinical efficacy in all groups of patients with visual loss in LHON and therefore the overall licensed population is appropriate to include in the scope. Chiesi will assess whether there are any pre-specified subpopulations of the clinical efficacy data in which idebenone demonstrates greater clinical effectiveness and therefore may be relevant for consideration.<br>**Would idebenone be a candidate for managed access?** | Comment noted. |

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| | | No. The clinical benefits of idebenone in LHON have been previously established as idebenone has demonstrated improvements in VA in the RHODOS and RHODOS-OFU clinical studies, as well as the Expanded Access Program, LEROS and PAROS real-world evidence studies. Idebenone has also already been recommended for the treatment of LHON in Scotland and Wales. Therefore, a managed access scheme is unlikely to collect additional evidence to address uncertainties in the clinical evidence. Additionally, there are no planned or ongoing trials which would report data within a managed access timeframe.<br><br>**Do you consider that the use of idebenone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br><br>**Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**<br><br>The QALY calculation in the economic modelling will consider the costs and benefits of idebenone in patients for the treatment of vision loss due to LHON. However, due to the severe impact of LHON on patients' quality of life, it is also expected that the introduction of idebenone is likely to result in substantial benefits outside of the QALY calculation.<br><br>LHON mostly presents in young adults, typically in the second and third decades of life[17], at a time when patients are expected to be in full-time employment or beginning their careers. Patients with LHON tend to also have young families to support. The disease often causes patients to work reduced hours, for lower wages and can encourage early retirement, all which contribute to productivity losses.[10]<br><br>The introduction of idebenone promotes recovery of vision loss and is proven to be effective in preventing further vision loss in some patients. When used early in acute patients, idebenone has the potential to stabilise or recover VA | Comment noted.<br><br>Comment noted. All relevant evidence will be taken into account by the committee when making its decisions. |

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| | | and in chronic patients it can reactivate viable but dormant RGCs and recover VA. These benefits are expected to allow patients the opportunity to continue both work and education, participate in routine activities and contribute to society.<br><br>Furthermore, the effects of idebenone treatment on extraocular features of LHON (LHON plus) such as cardiac conduction defects and neurological and skeletal abnormalities are not considered in the QALY calculation.<br><br>Additionally, idebenone can benefit carers of patients with LHON by reducing the burden of care for patients with vision loss due to LHON. In a recent study by Williams *et al.* (2023)[18], qualitative findings reported a substantial burden for many carers and family members of patients with LHON. The study reported major emotional impact, especially in mothers, who experienced immense guilt for passing on a gene that caused their child's vision loss. Carers of patients with LHON also experienced an impact on their social life and relationships, work and career and finances. [18] This highlights the challenges for a family of a patient with LHON.<br><br>The introduction of idebenone provides life-changing benefits to carers by improving patient outcomes. This in turn is expected to reduce the time needed by carers to support their family member, ease the emotional burden and allow more time for carers to pursue a social life and career.<br><br>The introduction of idebenone is also likely to result in a reduction in indirect costs associated with the costs of informal caregivers.<br><br>In a clinician survey conducted by Chiesi (2022),[19] clinicians reported that the percentage of patients needing informal caregiver support and the number of days a caregiver is needed are both increased with increasing LogMAR values. This demonstrates the value of idebenone in reducing the indirect costs of informal carers via improved efficacy. | |

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| | | The impact idebenone has on the wider societal perspective, the impact on extraocular features of LHON and QoL of carers of patients with LHON are not included in the QALY calculation and should therefore be considered qualitatively. | |
| | GenSight Biologics SA | Where do you consider idebenone will fit into the existing care pathway for LHON?<br><br>*We anticipate that idebenone will be prescribed to patients once the LHON diagnosis has been confirmed by genetic testing*.<br><br>Would idebenone be a candidate for managed access?<br><br>*Yes we believe idebenone would be a candidate for a managed access initiative, possibly to provide data on the long term treatment effects and optimal treatment duration.*<br><br>Do you consider that the use of idebenone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?<br><br>*LHON has been associated with a greater prevalence of smoking, excessive alcohol consumption and psychiatric comorbidities, and high rates of depression and anxiety have been reported in quantitative studies. Examination of Hospital Episode Statistics (HES) could provide this data. Availability of idebenone may help mitigate the conditions described above.* | Comment noted. No action required.<br><br>Comment noted<br><br>Comment noted.<br><br>Comment noted. |

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| | | *Increasing an individual's visual acuity will also provide societal benefits as an individual may be able to continue working or return to work.* | |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | **Where do you consider idebenone will fit into the existing care pathway for LHON?**<br>Raxone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON) and we consider the evidence that all patients should be offered the opportunity to benefit from this drug.<br>**Have all relevant comparators for idebenone been included in the scope? Which treatments are considered to be established clinical practice in the NHS for LHON in England?**<br>All relevant comparators are listed<br>**Are the outcomes listed appropriate? Should outcomes related to the non-vision related symptoms of LHON be included?**<br>Idebenone is not indicated for other symptoms and thus we expect just outcomes that are vision related (including quality of life) to be appropriate.<br>**Are there any subgroups of people in whom idebenone is expected to be more clinically effective and cost effective or other groups that should be examined separately?** | Comment noted. No action required.<br>Comment noted.<br>Comment noted.<br>Comment noted. |

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| | | Every person living with or diagnosed with LHON should have access to this drug and thus suspect that subgrouping would continue current inequity in the U.K.<br>**Would idebenone be a candidate for managed access?**<br>No, further obstacles and/or delay is inappropriate for people living with LHON | Comment noted. |
| | The Lily Foundation | None | No action required |
| | Genetic Alliance UK | No comments | No action required |
| Additional comments on the draft scope | Chiesi Farmaceutici S.p.A | No comments | No action required |
| | GenSight Biologics SA | Consider including stopping criteria for non-responders. | Comment noted. No action required. |
| | Leber's Hereditary Optic Neuropathy (LHON) Society | No comments | No action required |

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| | The Lily Foundation | As a patient organisation we feel very strongly that Idebenone should be considered for evaluation by NICE. We see first-hand the devastating effect that a diagnosis of LHON has on the lives of patients and families, with the rapid onset of the disease having a massive impact in terms of the health and quality of life of those it affects. We also hear anecdotal evidence from patients and families who have been able to access Idebenone and who feel it has allowed them to regain significant quality of life and give them back some independence.<br><br>The current inequity of access across the regions of the UK feels deeply unfair for patients living in England, some of whom are accessing Idebenone privately and others who are unable to do so because of the cost of accessing this treatment. Because Idebenone is not a mutation-specific treatment, we believe it offers a cost-effective, easy to administer treatment that could provide a glimmer of hope to those patients in the UK who are currently facing a diagnosis of LHON with its devastating and progressive pattern of natural history.<br><br>Thank you for your consideration. | Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: Project information \| Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over ID547 \| Guidance \| NICE |
| | Genetic Alliance UK | No comments | No action required |

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

Royal College of Pathologists
Macular Society