**National Institute for Health and Care Excellence**

**Highly Specialised Technologies Evaluation**

**Cerliponase alfa for neuronal ceroid lipofuscinosis type 2 [ID943]**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**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**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness | BioMarin | Appropriate | Comment noted. No action required. |
| | Evelina London Children's Hospital | Cerliponase alfa is a newly developed highly specialised medicine for the treatment of CLN2 Neuronal Ceroid Lipofuscinosis (NCL), also known as CLN2 disease, classic late infantile NCL, or classic late infantile Batten disease. I understand that BioMarin Pharmaceutical Inc are seeking licensing approval. Families affected by this disease have a strong voice (many are represented by the Batten Disease family Association) and are desperately looking for an approved treatment as fast as possible to be made available. It is therefore necessary and highly appropriate for NICE to evaluate this topic at this time. | Comment noted. No action required. |
| | Batten Disease Family Association (BDFA) | Please see specific comments on individual sections. | Noted. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Wording | BioMarin | Appropriate | Comment noted. No action required. |
| | Evelina London Children's Hospital | *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?*<br>Yes | Comment noted. No action required. |
| | BDFA | Please see specific comments on individual sections. | Noted. |
| Timing Issues | BioMarin | We would consider the urgency to be high given that CLN2 disease is a devastating disease which leads to the rapid and progressive loss of function and early death in childhood. | Comment noted. No action required. |
| | Evelina London Children's Hospital | CLN2 NCL disease is a very severe neurodegenerative disorder affecting children with no currently available disease modifying treatment. Reported initial results of a recently completely clinical trial at a number of professional and scientific research meetings (but I believe unpublished so far), suggest cerliponase alfa is effective and safe. There is an urgent need to clarify the position of NHS England with regard to the introduction of this new agent for families affected by the disease and their supporting professional teams. | Comment noted. No action required. |
| | Genetic Alliance UK | Currently there are no treatments available for the condition and there is significant unmet need. The evaluation is of particular urgency due to the speed at which the condition progresses with only a few years from onset of symptoms to the development of a vegetative state. For this reason it is important that patients in the UK are able to access the treatment as soon as possible after a license is granted. | Comment noted. No action required. |
| | BDFA | Neuronal ceroid lipofuscinosis type 2 (CLN2) is a rapidly progressing disease. Children lose their abilities very quickly after diagnosis. Cerliponase Alpha is the first treatment for this disease and is critically and urgently needed to | Comment noted. No action required. |

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| | | address the needs of families living with this devastating condition. | |
| Additional comments on the draft remit | Evelina London Children's Hospital | I would hope that the manufacturer would make available all relevant safety and efficacy data for independent review as part of this process. | Comment noted. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | BioMarin | Background information is unclear and not focused on CLN2 disease, mixing disease elements from other NCLs. The prevalence data seems not focused on CLN2 and is not consistent with understanding within BioMarin or the Batten Disease Family Association patient support group.<br><br>The description mixes definitions of infantile, late infantile and juvenile CLN2. In the UK the vast majority of cases of CLN2 disease are late infantile: 79 out of 81 cases of CLN2 disease in the international DEM-CHILD registry are late infantile NCL (http://www.dem-child.eu/index.php/wp03-epidemiology-natural-history.html Table 2). | Comment noted. Thank you for the information. The background section of the scope is intended to be a very brief summary of the disease and current treatment options. Further details about the disease and the impact on children with the disease and their families will be gained during the appraisal process. NICE has updated the background section for accuracy and to avoid ambiguity. |
| | Evelina London Children's | **Disease phenotype (paragraph 2):** Children may present with early delayed language development in the second year of life, but usually come to medical | Comment noted. Thank you for the information. |

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| | Hospital | attention with the onset of seizures between 2 and 4 years of age. Despite symptomatic treatment, the disease progresses with loss of play, mobility, language and feeding skills over a few years. Visual loss occurs late. Children are usually completely dependent on carers by the age of 6-7 years. Behaviour may be challenging early. Anxiety and frustration are probably common, but difficult to identify and assess. Death is inevitable between 6 and 13 years. There are exceptional cases where disease progression is slower and life expectancy extends to late teenage or early adulthood.<br>**Incidence and prevalence (para 3):** BPNU surveillance data suggests around 3-4 children are diagnosed with CLN2 NCL disease each year in the UK. Prevalence figures are unknown. I currently see 7-8 children aged between 3 and 18 years with this condition in my clinic, coming mainly from the south of England, and am aware of several more. I would estimate that there are no more than 30 affected children in the UK.<br><br>**Current treatment (para 4):** Current treatment does not aim to delay onset of disease symptoms. Current medical management aims to control symptoms following a palliative care model, maintaining function as far as possible and working holistically with child, family and all professional/supportive agencies. Medical treatment is especially challenging in this group given the complexity of symptoms, complex medication regimes, drug interactions, neurodisability related complications (drooling, spinal scoliosis and orthopaedic problems etc) and changing nature of the condition with time. | The background section of the scope is intended to be a very brief summary of the disease and current treatment options. Further details about the disease and the impact on children with the disease and their families will be gained during the appraisal process. NICE has updated the background section for accuracy and to avoid ambiguity. |
| | Genetic Alliance UK | According to the Batten Disease Family Association 5-6 children are diagnosed with CLN2 each year in the UK. They estimate there are between 30 and 50 affected children in the UK. This is slightly more than the number estimated by the company. | Comment noted. Thank you for the information. The background section of the scope is intended to be a very brief summary of the disease |

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| | | | and current treatment options. Further details about the disease and the impact on children with the disease and their families will be gained during the appraisal process. NICE has updated the background section for accuracy and to avoid ambiguity. |
| | BDFA | Paragraph 2 contains statements which are relevant to other forms of the NCLs and not CLN2. Ref BDFA CLN2 Late Intantile leaflet www.bdfa-uk.org.uk PDF is attached to this document<br>Children with CLN2 do not experience hallucinations or challenging behaviours.<br>Children appear to be healthy and developing normally for the first few years of life.<br>Towards the end of the second year, developmental progress may begin to slow down and some children will be delayed in the development of language skills.<br>Towards the end of the second year, developmental progress may begin to slow down and some children will be delayed in the development of language skills.<br>The first significant sign of the disease is usually the onset of epilepsy. The seizures may be varying in nature and include drops, vacant spells (absences) or motor seizures with violent jerking of the limbs and loss of consciousness. Initially, seizures may be successfully managed with medication for several months, yet they will always recur and often become difficult to control. | Comment noted. Thank you for the information. The background section of the scope is intended to be a very brief summary of the disease and current treatment options. Further details about the disease and the impact on children with the disease and their families will be gained during the appraisal process. NICE has updated the background section for accuracy and to avoid ambiguity. |

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| | | Children tend to become unsteady on their feet and may frequently fall.<br>Gradually, skills related to walking, playing and speech are lost with children becoming less able and increasingly dependent.<br>By 4 - 5 years of age, children with late-infantile CLN2 disease usually have myoclonic (rapid involuntary muscle spasm) jerks of their limbs and are prone to erratic movements of their head (nods).<br>They may have difficulty sleeping and often become distressed around this time, usually without obvious reason.<br>Their vision gradually deteriorates, with its loss being inevitable.<br>By the age of 6 years, most<br>By the age of 6 years, most children will be completely dependent on families and carers for all of their daily needs. In order to ensure they receive adequate nutrition, they may require a specialist feeding tube (gastrostomy).<br>There may be noticeable stiffening of their arms and legs, whilst some children become prone to frequent chest infections.<br>Although there is a general progression of symptoms associated with late-infantile CLN2 disease, it is impossible to state the exact rate or pattern of this as each child and situation is unique. Sadly most children who have late infantile CLN2 disease die between the ages of 6 and 12 years, though there are exceptions.<br>The statement of 49 admissions for NCLs in England is both irrelevant and unhelpful in describing the prevalence and incidence of the disease in England.<br>We estimate between 5 and 6 new diagnoses per year.<br>In England we know of no children who do not have the classic form of the disease.<br>The background does not identify that as a genetic disease and because of later diagnosis families may have more than 1 affected children.<br>We are in contact with a 3 families in the UK who have two affected children.<br>There may of course be other families who are not in touch with the BDFA.<br>The background does not identify the multidisciplinary team of health, | |

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| | | education and social care professionals involved with children with CLN2 disease:<br>Currently there is no cure for CLN2 disease. Therefore, appropriate and effective symptom management is essential to assist in maintaining a good quality of life for children and their families.<br>Holistic support for parents, siblings and wider family members is vital throughout the journey<br>Epilepsy can be difficult to treat and therefore attaining complete control of seizures is not always possible.<br>Anticonvulsant medications (e.g. sodium valproate) will be necessary from the early stages of the disease process. It is recommended that drugs such as carbamazepine, phenytoin and vigabatrin are avoided. Myoclonic jerks (involuntary muscle spasms) are common, though should not be confused with epileptic seizures.<br>They can interfere with rest and sleep as well as being distressing for children and their families. Levetiracetam has demonstrated positive effects in a combined action against myoclonic jerks and seizures.<br>Spasticity (unusually tight or stiff muscles) can be managed with baclofen and/or trihexyphenidyl. In order for medication to be sufficient the responsible doctor may need to prescribe<br>higher dosages than are usual for those who do not have CLN2 disease.<br>A multidisciplinary team of professionals including doctors, nurses, physiotherapists, occupational therapists, sensory specialists, speech and language therapists should be involved in the care of children and young people with CLN2 disease at all stages of the disease.<br>Although their required levels of input may vary at various periods, they should work collaboratively and in conjunction with the family to appropriately meet the needs of the child and those caring for them. Support will be needed for a range of issues including progressive difficulties with chewing and swallowing, constipation, hydration, respiratory function, oral secretions, motor disorder, sleep disturbance and visual impairment. | |

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| | | Attention to posture, seating, skin and mouth care is essential and children will require additional nutritional support that may include consideration of a gastrostomy.<br>Referral for support from local Continuing Care Nursing Teams, Children's Hospice and Community Palliative Care teams are recommended. These teams can provide a variety of services supporting the child and other family members. | |
| The technology/ intervention | BioMarin | Please amend the following:<br>Current: "It is administered by intracerebroventricular infusion every 2 weeks over a 48-week treatment period"<br>Proposed: "It has been studied in a 48-week Phase 1/2 open label trial and ongoing extension study in which it is administered by intracerebroventricular infusion every 2 weeks, it is anticipated that the treatment will be for life"<br>Rationale: The treatment period is not limited to 48 weeks. This was the length of the evaluation period of the pivotal trial.<br>Current: "It has been studied in patients with a confirmed diagnosis of late-infantile CLN2 and with mild to moderate disease as documented by a two-domain score of 3-6 on motor and language domains of the Hamburg Scale, with a score of at least 1 in each of these two domains"<br>Proposed: "It has been studied in patients with a confirmed diagnosis of late-infantile CLN2 and with disease in the rapid progression phase as documented by a two-domain score of 3-6 on motor and language domains of the Hamburg Scale at trial inclusion, with a score of at least 1 in each of these two domains. At evaluation phase baseline patients had scores between 1 and 6 points on motor and language domains of the Hamburg Scale"<br>Rationale: The treatment has been studied in patients with a range of disease progression. Baseline scores of 1 to 6 on the 0 to 6 point CLN2 clinical rating scale. There is no mild to moderate disease, there are different phases in the | Comment noted. NICE has updated this portion of the scope to avoid ambiguity to reflect accuracy of the proposed marketing authorisation. |

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| | | progression of disease. | |
| | Evelina London Children's Hospital | *Is the description of the technology or technologies accurate?*<br>Yes, to my knowledge | Comment noted. No action required. |
| | Genetic Alliance UK | The scope states that the medicine is administered every two weeks over a 48-week treatment period. However, we understand that although the main clinical trial lasted 48-weeks, as this is an enzyme replacement therapy and not a cure, affected individuals would be expected to remain on the treatment indefinitely. | Comment noted. NICE has updated this portion of the scope to avoid ambiguity to reflect accuracy of the proposed marketing authorisation. |
| | BDFA | No comment | Noted. |
| Population | BioMain | The population is not defined appropriately. Cerliponase alfa has been studied in children with a range of disease progression. Baseline scores of 1 to 6 on the 0 to 6 point CLN2 clinical rating scale. Therefore the population should be all patients with a confirmed diagnosis of CLN2. | Comment noted. NICE have taken this into consideration and amended the scope to reflect the relevant population. |
| | Evelina London Children's Hospital | Confirmed diagnosis of CLN2 NCL disease: TPP1 enzyme deficiency, 2 disease causing alleles identified in CLN2. It will be essential to clearly define clinical entry and exclusion/exit criteria for treatment (mild to moderate disease is too vague) | Comment noted. NICE have taken this into consideration and amended the scope to reflect the relevant population. |
| | Genetic Alliance | Throughout the scope references are made to CLN2, late infantile CLN2, and late infantile Batten disease as if they are equivalent, but this is not the case. | Comment noted. NICE |

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| | UK | Although historically NCLs were categorised bay age of onset, the nomenclature has recently been revised to reflect the developing understanding of the genetic basis of the conditions. Neuronal ceroid lipofuscinosis type 2 (CLN2), which involves a deficiency of TPP1, is usually late infantile in onset, but is sometimes of juvenile onset.<br>Similarly, most late infantile onset Batten disease is due to mutations in the CLN2 gene (encoding TPP1), but a small percentage is due to mutations in the CLN5, CLN6, CLN8, MFSD8 and CLN1 (PPT1) genes.<br>Cerliponase alfa is a TPP1 enzyme replacement therapy, and so would only be expected to be effective in patients with a TPP1 deficiency. CLN2 refers to CLN caused by mutation in the CLN2 gene, regardless of the age at onset. However, it might be expected that the subpopulation of patients with CLN2 disease of onset other than late infantile might respond slightly differently.<br>It is not clear at this stage whether the marketing authorisation will be limited to patients with mild to moderate disease, as was the case for one of the two clinical trials. The trial also excluded patients whose seizures were not stable. However, if the license were to include patients with severe disease or uncontrolled seizures, these sub groups should be considered separately. | have taken this into consideration and amended the scope to reflect the relevant population. |
| | BDFA | This should also be considered for children who are asymptomatic as is the case for siblings who are diagnosed as a result of their older sibling's symptomatic diagnosis. | Comment noted. NICE have taken this into consideration and amended the scope to reflect the relevant population. |
| Comparators | BioMarin | Please amend the following:<br>Current: Established treatment for symptoms and palliation<br>Proposed: NHS care for CLN2 patients without cerliponase alfa<br>*Rationale: Comparator should consider current NHS care without cerliponase* | Comment noted. NICE has taken into consideration your comment to ensure the comparators in the scope reflect the most |

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| | | *alfa which will bring the assessment in scope otherwise additional non NHS elements can be integrated* | up-to-date clinical practice. |
| | Evelina London Children's Hospital | Best alternative care – multidisciplinary/multiagency symptom control for epilepsy; movement disorder; discomfort; feeding and nutrition; mobility and positioning; lifting and handling; sleep; vision; family respite and end of life care. | Comment noted. NICE has taken into consideration your comment to ensure the comparators in the scope reflect the most up-to-date clinical practice |
| | BDFA | Would require further clarification of what this "standard of care" is. | Comment noted. NICE has taken into consideration your comment to ensure the comparators in the scope reflect the most up-to-date clinical practice. |
| Outcomes | BioMarin | We would propose to add the following outcomes:<br>- Visual function<br>- Seizures<br>- Myoclonus<br>- Feeding<br>- Dystonia<br>- Productivity | Comment noted. NICE has taken into consideration your comment to amend the outcomes to accurately reflect values most important to assess efficacy of treatment and impact on quality-of-life. |

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| | | - Hospitalisations/ICU care/Emergency room care<br>- Medication<br>- Home adaptation<br>- Surgery | |
| | Evelina London Children's Hospital | As well as safety and efficacy outcomes, there is a need to include some measure of burden of care on families as this highly specialised medical treatment is invasive, technology dependent and very demanding on family's time as well as health service provision. Quantitative outcome measures might include Hamburg scale (particularly motor and language subscales), measurement of cortical volume on serial Brain MRI, A&E attendances and hospitalisations, prescriptions, school attendance rates | Comment noted. NICE has taken into consideration your comment to amend the outcomes to accurately reflect values most important to assess efficacy of treatment and impact on quality-of-life. |
| | Genetic Alliance UK | Unlike many rare diseases, the natural history of CLN2 is reasonably well understood, and there are a number of validated scales to measure disease progression. In addition to the Hamburg Motor and Language Scale mentioned, which was also used in the clinical trial, we understand that the Weill Cornell LINCL Scale and the Unified Batten Disease Rating Scale are also commonly used, and may perhaps be more sensitive to small changes in CNS function and early stage deterioration. Whichever scale or combination of scales is chosen, it will be important to ensure that all outcomes of importance to patients and their families are considered, including those primarily relating to quality of life. waht | Comment noted. NICE has taken into consideration your comment to amend the outcomes to accurately reflect values most important to assess efficacy of treatment and impact on quality-of-life. |

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| | BDFA | There are other outcome measures that<br>are not included here:<br>1. Measures of changes in visual impairment.<br>2. Hospitalisation is too broad a measure and doesn't identify the other clinical factors<br>a. Change in medication consultations<br>b. A&E admissions<br>c. GP consultations<br><br>This section does not identify the enormous burden on the carers and families of caring for children with this condition.<br>1. Physical impact on carers health<br>2. Impact on carers mental health<br>3. Impact of the disease on family breakdown<br>4. Financial and employment impact on family<br>5. Specialist equipment and adaptations<br>6. Impact on siblings<br>7. Impact on wider family including grandparents who also take on caring roles.<br><br>We believe that this new therapy will improve earlier diagnosis<br>There is currently no NCL service in England. Patients are seen by local teams, depending on geographical location. Those teams may consult/refer with LSD centres but patients do not routinely have their care managed at these centres. The onset of this therapy, we believe, we improve access to specialised centres for families and to improved centralised, MDT care. | Comment noted. NICE has taken into consideration your comment to amend the outcomes to accurately reflect values most important to assess efficacy of treatment and impact on quality-of-life. |
| Equality and Diversity | BioMarin | No anticipated impacts on equality.<br><br>BioMarin supports treatment for all patients who can benefit, any limitation needs to be considered by the NHS England, English Clinical and Patient Experts. | Comment noted. No action required. |

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| | Evelina London Children's Hospital | CLN2 neuronal ceroid lipofuscinoses affects all ethnic and cultural groups. | Comment noted. No action required. |
| Other considerations | BioMarin | We would like to add that cerliponase alfa is likely to have significant benefits other than health. These benefits include education, mental health, employment, societal contribution. Similar benefits should be considered for carers and the families of patients who will be able to benefit society by improved employment and family life.<br><br>Discussion about creating an NHS service specification for NCLs given there is not dedicated current service in England. | Comments noted. No action required. |
| | Evelina London Children's Hospital | Cerliponase alfa is in my view unlikely to return affected symptomatic children to full health and normal life expectancy given the nature of the condition. It may however have the potential to extend life expectancy for many years with ongoing symptoms, medical and educational needs and a varying degree of neurodisability. The long term prognosis for treated children is of course unknown. It is likely that children living longer will develop additional late medical problems which are not yet currently evident. Cardiac, gut and pancreatic function are likely to be impaired by the pathological disease process and may not be effectively treated by intracranial delivery of cerliponase alfa. | Comments noted. No action required. |
| Innovation | BioMarin | Cerliponase alfa is the first treatment specific to addressing the underlying cause of CLN2 disease and the first enzyme replacement therapy to be delivered via intracerebroventricular (ICV) infusion. The clinical benefit in stabilising disease progression in 65% of patients in the clinical study represents a 'step-change' in the management of this devastating neurological condition and is anticipated to have a significant benefit to | Comment noted. No action required. |

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| | | patients and caregivers | |
| | Evelina London Children's Hospital | Yes, this treatment and its method of delivery are innovative and represent a huge step-change forward for this condition and also potentially for other neurological and neurodegenerative conditions. | Comment noted. No action required. |
| | Genetic Alliance UK | This would be the first treatment to address the underlying cause of the condition and to slow and perhaps even reverse the deterioration.<br>The ability of the enzyme replacement to act directly on the brain also seems to be innovative. | Comment noted. No action required. |
| | BDFA | This is very much a step-change in the management of the condition as no previous treatments exist. Current standard of care is palliative. | Comment noted. No action required. |
| Questions for consultation | BioMarin | Q: How is a diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed?<br>A: Either demonstration of a) deficient TPP1 enzyme activity in leukocytes or fibroblasts, or b) detection of two pathogenic mutations in trans is diagnostic for CLN2 disease. *Reference: Fietz et al. Molecular Genetics & Metabolism. In press.* http://dx.doi.org/10.1016/j.ymgme.2016.07.011<br><br>Q: How is late-infantile CLN2 disease defined? Would cerliponase alfa be used in children with early-infantile CLN2 disease?<br>A: All clinical trial patients had late-infantile forms of CLN2 disease, which is defined as patients who present with symptoms between the ages of 2-4 years. In the DEM-CHILD international registry of 81 patients with CLN2 disease, 79 reported as having the late-infantile form. It would be anticipated that ERT treatment with cerliponase alpha can benefit patients with early-infantile CLN2 disease as well.<br><br>Q: How is disease severity defined? Is there an established measurement | Comment noted. Scope has been updated in the relevant sections. |

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| | | for CLN2 disease severity? Would cerliponase alfa be used in children with severe CLN2 disease?<br>A: Disease severity is not defined, as all CLN2 patients suffer from severe disease manifestations. Disease progression may be considered in terms of loss of function as captured by clinical rating scales such as the Hamburg scale. As stated above, cerliponase alfa has been studied in children with a range of disease progression (between 1 and 6 on the CLN2 clinical rating scale) where patients across the disease spectrum showed benefit. Cerliponase alfa has the potential to benefit patients across the spectrum of disease.<br><br>Q: Which treatments are considered to be established treatment for symptoms and palliation for neuronal ceroid lipofuscinosis type 2?<br>A: There are no established treatments for CLN2, however established international protocols recommend the following treatments for different symptoms:<br>**Seizures** – Valproate, clobazam, levetiracetam, lamotrigine, zonisamide and phenobarbital; most commonly used is valproate in various add-on combinations<br>**Myoclonus** - Lamotrigine, zonisamide, phenobarbital, levetiracetam, valproate<br>**Spasticity** - Baclofen, tizanidine, THC, diazepam, phenobarbital<br>**Dystonia** - Tizanidine, baclofen, benzodiazepines, trihexyphenidyl<br>**Secretions** - Inhaled ipratropium bromide, atropine, glycopyrolate scopolamine (hyoscine)<br>**Pain** - Simple analgesia (paracetamol, NSAIDs); stronger analgesics (methadone, morphine, hydromorphone); other (gabapentin, clonidine, pregabalin, amitriptyline)<br>**Breathing difficulties** - Salbutamol<br>**Mucus** - Dornase alfa | |

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| | | There is wide use of additional care not limited to personally adapted wheelchairs and mobility aids, home adaptations, surgery, social care, physiotherapy, speech therapy. The above list is not comprehensive and the final assessment will integrate the clinical perspective on English current care.<br><br>Q: Are there any subgroups of people in whom cerliponase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?<br>A: No subgroups are anticipated: Cerliponase alfa has been shown to stablise the CLN2 rating scale score in patients across a spectrum of disease progression | |
| | Evelina London Children's Hospital | Cerliponase alfa should only be used for this disease casued by mutations in the CLN2 gene. Other genetic types of NCL (Batten disease) would not be expected to respond to this treatment.<br><br>There is no national service, agreed standards of care or consensus clinical guidelines for children diagnosed with CLN2 disease. A BDFA sponsored survey performed many years ago suggested inequalities in service provision over the UK and a high degree of unmet need perceived by families. A proposal for a Nationally Commissioned Service prepared jointly by the BDFA and Guy's and St Thomas' NHS Foundation Trust was unsuccessful in 2009-10. Many children are referred to the Evelina London Children's Hospital for expert advice and ongoing care is shared between local Paediatric Services and the Evelina team.<br><br>It would be expected that young affected pre-symptomatic siblings would gain | Comment noted. Scope has been updated in the relevant sections. |

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| | | most if the treatment was given early, because good function and skills might be maintained, but this has not so far been tested. Older children with more challenging symptoms who have already lost communication and mobility skills may have less to gain from such a treatment, but this has not been tested. | |
| | BDFA | *'How is a diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed?'*<br><br>1. All families in the UK should have diagnosis via blood test, enzyme levels and mutational analysis.<br><br>'*How is late-infantile CLN2 disease defined? Would cerliponase alfa be used in children with early-infantile CLN2 disease?'*<br><br>2. We believe that it should be used in children who are asymptomatic/early stages of the disease and also those children in later stages of the disease.<br><br>*'How is disease severity defined? Is there an established measurement for CLN2 disease severity? Would cerliponase alfa be used in children with severe CLN2 disease?'*<br><br>3. Disease severity is defined according to the Hamburg and Weill-Cornell scales.<br>*'Is the comparator for cerliponase alfa defined appropriately in the scope?'*<br><br>4. Questions re the comparator are covered in the previous sections.<br><br>*'Which treatments are considered to be established treatment for* | Comment noted. Scope has been updated in the relevant sections. |

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| | | *symptoms and palliation for neuronal ceroid lipofuscinosis type 2?'*<br><br>5. Established treatments for symptoms are covered in the previous sections<br><br>'*Are there any subgroups of people in whom cerliponase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?'*<br><br>6. Treatment of children earlier in the disease (and earlier diagnosis) will have significant clinical, health, financial and social care benefits to them and the whole family<br><br>'*Are the outcome measures listed in the scope appropriate? Is there any other relevant outcome measure that should be included?'*<br><br>7. Outcome measures are considered in the previous section.<br><br>*'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'.*<br>8. There are no equality issues | |
| Additional comments on the draft scope | BioMarin | Given the nature and severity of the disease BioMarin supports a move towards a speedy resolution of access to patients. It would be good to directly recommend early discussions between NICE, NHS England, clinical experts and patient support groups about the application of a managed access program in parallel with the NICE evaluation | Comment noted. No action required. |

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

Department of Health