NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technology Evaluation

Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of cerliponase alfa within its licensed indication for treating neuronal ceroid lipofuscinosis type 2 for national commissioning by NHS England.

Background

Neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare genetic disease caused by the deficiency of an enzyme called tripeptidyl peptidase1 (TPP1). CLN2 is one form of neuronal ceroid lipofuscinosis (NCL), also known as Batten disease. CLN2 disease is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the CLN2 gene, and both parents are unaffected carriers. [1] A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells. Accumulation of these proteins and lipids prevent the cells from functioning as they should. CLN2 is characterised clinically by a decline of mental and other capacities, epilepsy, and vision loss through retinal degeneration, and histopathologically by intracellular accumulation of ceroid lipofuscin in the neuronal cells of the brain and retina.[2]

Children with CLN2 are healthy and develop normally for the first few years of life, although emerging literature suggests that language is usually delayed around 18- 24 months of age. The disease then progresses rapidly beginning with increasing visual impairment resulting in blindness, complex epilepsy with severe seizures that are difficult to control, rapid involuntary muscle spasm, jerks of limbs, difficulties sleeping, the decline of speech, language and swallowing skills, and a deterioration of motor skills that result in the loss of mobility. Ultimately the child or young person will become totally dependent on families and carers for all of their needs. Other symptoms that are commonly experienced include hallucinations, memory loss and challenging behaviours. Death is inevitable and usually occurs between the ages of 6 and 12 years.

The exact prevalence and incidence of this group of disorders are unknown. In 2013-14, there were 49 admissions for NCLs in England.[3] An epidemiological study into neurological deterioration in childhood identified 141 cases of NCL (all forms) in the UK over a 12 year period.[4] The Batten Disease Family Association estimates that about 1-3 children are diagnosed with an infantile form of Batten disease and approximately 7-10 children are diagnosed with the late-infantile form each year in the UK. This equates to about 15-30 children and 30-60 children affected by early and late onset

NCLs in the UK, respectively. A minority of patients with the late infantile form of Batten disease may not have CLN2 disease, and conversely not all patients with CLN2 disease have the late infantile form. With these factors considered, as well as the given life expectancy range, the company estimate there are approximately 19 to 38 patients in the UK living with the CLN2 associated form of NCL.[5]

There is currently no curative treatment for CLN2. Treatment options are currently symptomatic and palliative only, aiming to delay onset and improve quality of life. Seizures, malnutrition, gastroesophageal reflux, pneumonia, depression, anxiety, spasticity, Parkinsonian symptoms, and dystonia can be effectively managed through medication and physical therapy.[6] Prevention, monitoring and managing of complications (due to immobility and loss of function) is also recommended (for example, management of malnutrition, gastroesophageal reflux and aspiration pneumonia).[5]

Children often receive a multiple medications and clinicians need to balance symptom control with the adverse effects of treatment interactions. Early in the disease, therapies are administered in an attempt to prolong function, but treatment goals soon evolve to supporting quality of life.

The technology

Cerliponase alfa (brand name unknown, BioMarin) is a recombinant human tripeptidyl peptidase 1 which is an enzyme replacement therapy. It is administered by intracerebroventricular infusion every 2 weeks over a 48-week treatment period.

Cerliponase alfa does not have a UK marketing authorisation for treating neuronal ceroid lipofuscinosis type 2. 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.

Intervention(s)	Cerliponase alfa
Population(s)	Children with a confirmed diagnosis of CLN2 and with mild to moderate disease.
Comparators	Established treatment for symptoms and palliation
Outcomes	The outcome measures to be considered include: • changes in CLN2 disease clinical measures • motor and language function • hospitalisation (including admissions to intensive care units) • mortality

	• adverse effects of treatment (including immune response) • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Impact of the new technology	• clinical effectiveness of the technology • overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• budget impact in the NHS and PSS, including patient access agreements (if applicable) • robustness of costing and budget impact information • technical efficiency (the incremental benefit of the new technology compared to current treatment) • productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used) • allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • staffing and infrastructure requirements,

	including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England Manual for prescribed specialised services, service 71: lysosomal storage disorder service (adults and children), November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf NHS England Standard Contract for Lysosomal Storage Disorders Service (Children), 2013. http://www.england.nhs.uk/wp-content/uploads/2013/06/e06-lyso-stor-dis-child.pdf

Questions for consultation

How is a diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed?

Cerliponase alfa has been studied in patients with a confirmed diagnosis of late-infantile CLN2 and with mild to moderate disease.

- How is late-infantile CLN2 disease defined? Would cerliponase alfa be used in children with early-infantile CLN2 disease?

- 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?

Is the comparator for cerliponase alfa defined appropriately in the scope?

Which treatments are considered to be established treatment for symptoms and palliation for neuronal ceroid lipofuscinosis type 2?

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?

Are the outcome measures listed in the scope appropriate? Is there any other relevant outcome measure that should be included?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the

proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cerliponase alfa is licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: http://www.nice.org.uk/media/DE4/9A/HSTCombinedInterimProcessMethods.pdf.

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1 Batten Disease Family Association. CLN2 disease, late infantile. www.bdfa-uk.org.uk/cln2-disease-late-infantile/. Accessed 18 August 2015.

2 Orphanet. Neuronal Ceroid Lipofuscinosis. www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=216. Accessed 19 May 2016.

3 Health & Social Care Information Centre. Hospital episode statistics for England. Inpatient statistics, 2013-14. www.hscic.gov.uk Accessed 18 August 2015.

4 Verity C, Winstone AM, Stellitano L *et al*. The epidemiology of progressive intellectual and neurological deterioration in childhood. Archives of Disease in Childhood 2010;95:361–364.

5 Company provided information.

6 Mole SE and Williams RE. Neuronal Ceroid-Lipofuscinosis. GeneReviews[Internet]. www.ncbi.nlm.nih.gov/books/NBK1428/. Accessed 18 August 2015.