8 March 2019

Dr Rosie Benneyworth
Vice Chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Dr Benneyworth

Re: Final Evaluation Determination – Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2

The Batten Disease Family Association (BDFA) hereby gives grounds that it would like to appeal against the Final Evaluation Determination for "Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2" on the following grounds:

Ground one: In making the assessment that preceded the recommendation, NICE has:

a) failed to act fairly

or

b) exceeded its powers

Ground two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Batten disease is a rare lysosomal storage disease. Enzyme replacement therapy has been suggested for lysosomal storage diseases, such as Fabry and Batten disease, since Christian de Duve's work in 1964[1]. Cerliponase alfa, also known as Brineura, is the first ever treatment for any of the 14 forms of Batten disease and has both FDA and EMA marketing authorisation approval. Not recommending Brineura for use by NHSE to treat children means that children with CLN2 are not receiving treatment that will prolong their lives and improve the quality of their lives. There are 20 other countries currently providing Brineura to their children with CLN2, including Wales. There are a tiny number of children in England with CLN2; the budget impact on the overall NHSE budget would be negligible. Children with CLN2 are incredibly vulnerable members of our society with complex needs and yet they bring joy to their families, friends and communities. It is public opinion that Brineura should be funded by NHSE as demonstrated by the BDFA's petition, which at the time of writing numbers over 359,000 signatures[2]. It is incumbent on NICE to evaluate the evidence fairly and reasonably and be able to demonstrate that it has done so.

[1] Fabry Disease: Perspectives from 5 Years of FOS, eds Atul Mehta, Michael Beck and Gere Sunder-Plassmann, Oxford: OxfordPharmaGenesis, 2006

[2] https://www.change.org/p/nhs-england-help-fund-the-only-treatment-for-children-with-fatal-batten-diesease?recruiter=856182787&utm_source=share_petition&utm_medium=copylink&utm_campaign=share_petition

The committee accepts that: *"CLN2 is a genetic disease that progresses rapidly, and leads to loss of speech, mobility and vision, progressive dementia and early death. Current treatment options are limited to symptomatic relief, and supportive and palliative care."*

The committee recognise that Brineura has benefits for the children with CLN2 and their families. This decision will make it impossible for children who are newly diagnosed to be offered the treatment. There are at least two families currently in England who have children with CLN2 who would like to receive treatment who are excluded from doing so. As families will do whatever they can for their children, it is probable that families will seek to relocate to other countries that give access to the treatment. Families connected to the Batten Disease Family Association (BDFA) are already exploring such options. In the current climate of uncertainty, achieving this will be extremely difficult for families, having a further detrimental impact on them and their mental health, and will mean that this decision is effectively contributing to the creation of a form of medical refugee.

NICE accepted that children with CLN2 have no alternative treatment options to Brineura. If they do not get access to Brineura, they will endure *"loss of speech, mobility and vision, progressive dementia and early death*". Children with CLN2 are severely disabled, therefore, have a protected characteristic. It appears that the drug evaluation discriminates against children who have additional legal protection.

Cerliponase alfa is the kind of innovative treatment that NHS's Genomic Medicine Service will need to offer patients. Children with Batten disease are often diagnosed through genetic testing. The GMS website states:

"The systematic application of genomic technologies has the potential to transform patient's lives by:

- *enabling a quicker diagnosis for patients with a rare disease, rather than years of uncertainty, often referred to in rare disease as the 'diagnostic odyssey'*[3]

It is futile and a waste of money to aspire to quicker diagnosis if treatments are going to be deemed not cost-effective.

Families agreed to their children's participation in the clinical trial because it offered them hope for a better future for their children. They did so in the hope and expectation that their health service would recognise the benefit of the treatment, if there was one, and fund it. Their bravery has had a huge contribution to the global battle against Batten disease.

The BDFA is the only charity working with families of children with Batten disease. We were formed by parents to offer support and information to other parents,

[3] https://www.england.nhs.uk/genomics/nhs-genomic-med-service/

because of lack of these within the health and social care system. On behalf of our brave parents, we raise a number of points that we believe show flaws in the decision-making process.

Ground 1: In making the assessment that preceded the recommendation, NICE has: (a) failed to act fairly

1a.1 NICE has acted unfairly in not including benefits that do not impact on the NHS within their calculations

It is unfair that NICE decided not to include the cost savings that would be of benefit to other parts of the health and social care system as specified in section 4.25 as health is meant to be increasingly integrated with social care following the Health Act 1999 and subsequent Acts. The cost benefits of the treatment felt in other parts of the system are true cost benefits and not double counting.

1a.2 It is unfair to use a system that disadvantages rare disease patients

The committee's judgement about the efficacy of Cerliponase alfa was extremely positive. The interim process and methods of the highly specialised technologies programme (2017) currently used by NICE and NHSE for pricing does not facilitate drug availability for patients. The current interim process appears to be inflexible. It disadvantages rare disease patients and their access to orphan drugs because, by definition, the companies that develop rare disease drugs are not able to reduce their prices dramatically due to the very low numbers of paying patients. This is unfair. This affects all rare disease drugs being offered to NHSE and all rare disease patients.

1a.3 The committee has taken decisions that do not take account of publicly available data that it would be reasonable for them to have referenced

The committee has not taken into account the additional costs families bear when raising a severely disabled child. It has been reported that it costs three times as much to bring up a disabled child than it does to raise a child with no disabilities[4]. There is recognised but not documented that there is a difference between raising a severely disabled child and a disabled child. The committee has not taken the impact of both the reported increased cost on families and the anecdotal difference. Many families tend to have at least one parent who stops working when their child is diagnosed with Batten disease and this

[4] https://www.dlf.org.uk/content/key-facts

would have an impact on their overall financial situation. To disregard this impact is unfair.

Ground 1: In making the assessment that preceded the recommendation, NICE has: (b) exceeded its powers

NICE is a public body and, therefore, bound to abide by human rights legislation. There are a number of relevant pieces of legislation. In the UN Convention of the Rights of Persons with Disabilities, Article 10 states that persons with disabilities have a right to life. Brineura offers children with CLN2 the opportunity to extend their lives with a good quality of life. By not recommending the drug, NICE is denying these children, especially those who do not have any access to the treatment, that right.

In addition, NICE is in breach of its own guidance *Guide to the methods of technology appraisal 2013,* which states: *"NICE is committed to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and society as a whole…*[5]*"* Children with CLN2 share a protected characteristic. By failing to recommend Brineura, NICE is pitting the children and their families, who are impacted by that protected characteristic, against the rest of the English population. This exceeds NICE's powers.

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 It is unreasonable for NICE to expect parents and families to live with the level of uncertainty of access to treatment this decision creates

Section 1.2 states that the recommendation is *'not intended to affect treatment with cerliponase alfa that was started on the NHS before this guidance was published.'* While it may be normal practice for patients who are benefiting from treatment through either clinical trials or compassionate use schemes, this depends on the goodwill of the pharmaceutical company; there is no right to continued access to that treatment. There have been at least one example in the past where a company has withdrawn an effective, life-saving treatment from the UK from patients (Dinutuximab beta). The pharmaceutical company is a private company and is not managed, owned or operated by NICE, NHSE, the BDFA or families of children with Batten disease. Therefore, they are at liberty to withdraw from this market at any time. This places an

[5] https://www.nice.org.uk/process/pmg9/chapter/introduction#fundamental-principles

additional enormous pressure on families. No evidence has been presented that guarantees continued access to treatment for those already receiving it, despite the committee has been presented with sufficient evidence so the it: *"…appreciated that CLN2 is a devastating condition, with a debilitating and life-limiting effect on children with the condition, and that it has a substantial and financial impact on their families."* It is not reasonable to acknowledge the devastation of the disease and the benefit of the treatment only not to recommend the treatment.

2.2 It is unreasonable to request long-term data and refuse to enter into a tool designed to produce that data

Families were consulted on the managed access agreement proposal on 27 Feb 2017 in a focus group as a means of ensuring that it would be acceptable to families. It was proposed by the company as a means to address concerns raised in early committee meetings about the lack of long-term data. It proposes that there is a commitment from all parties to record, monitor and review 'real world' data, i.e. data not collected under clinical trial restrictions, for five additional years. Families reviewed the proposal and were satisfied that it was feasible for them to commit to the conditions they would be under for their children to receive treatment. As the managed access agreement had been through this process, it is unreasonable for NICE to assert that it needs long-term data and refuse to implement the mechanism by which that data could be collected. The FED records that: *'The committee concluded that it was satisfied that the company's proposed data collection could address the clinical uncertainties that it had identified.'* It is not only unreasonable but illogical not to progress to that step in order to rectify concerns raised.

2.3 NICE has acted unreasonably by allowing children with CLN2 to participate in a clinical trial and to change the economic structures by which cost effectiveness will be judged partway through that process

The QALY thresholds by which treatments for rare diseases were changed in April 2017. This was several years through a process that has currently taken over five years. The clinical trial, itself, is due to end in 2020, which means it will be a five-year long trial, which is a substantial trial. It is unreasonable for NICE to change the standards by which cost effectiveness of the treatment would be judged part way through that clinical trial. It is feasible that the company might have made different decisions about entering the English market if the QALY thresholds had been at the current level. It is not reasonable to expect parents who agreed for their children to participate under one set of economic circumstances to be satisfied to have the

treatment for their children be judged, in effect, by rules that have been changed part-way through.

In addition, the use of any form QALY has been called into question by a range of academics, such as in the *Journal of Stem Cell Research and Therapy*[6] and *the Leonard Schaeffer Center for Health Policy and Economics*[7]

In the written submission from the Bioindustry Association in the current Health and Social Care Select Committee, they state:

"As more rare and ultra-rare disease medicines have gained central authorisation for use from the European Medicines Authority, it has become apparent that traditional cost-effectiveness measures are not appropriate for assessing medicines for rare and ultra-rare diseases. Specifically, it is not appropriate to use cost-per-QALY thresholds as an overarching criterion to evaluate rare and ultra-rare medicines. This is due to:

a) *Small patient populations, which make it difficult to enrol sufficient numbers of patients in clinical studies to generate significant data which meets payer expectations*

b) *The epidemiology of rare and ultra-rare diseases being less well understood, making projections of long-term benefit very difficult*

c) *The absence of alternative treatments, existing standard of care and/or the lack of robust data for comparators makes it very challenging to benchmark costs-effectiveness."*

It is not reasonable for NICE to use a system of evaluation that has been shown to be and widely recognised as flawed without paying due care to the families agreeing to participate.

2.4 It is unreasonable for NICE to take account of perceived administrative difficulties in their deliberations

During discussion about the proposed early diagnosis campaign to support the proposed managed access agreement, the committee stated that *'there are substantial administrative barriers to implementation'* [of the early diagnosis campaign]. Earlier diagnosis has an impact on the overall cost effectiveness of the treatment. It is, therefore, crucial to improve the diagnostic odyssey for children with CLN2. It is not reasonable for NICE to include that consideration as a factor as it is outside their remit as specified in NICE's Social Value Judgements. This specifies decisions should be made on clinical and cost effectiveness, not whether something is difficult to implement.

[6] https://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.php?aid=70859

[7] https://www.ispor.org/docs/default-source/presentations/1377.pdf?sfvrsn=6071348f_1

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2.5 NICE has acted unreasonably in judging Brineura by a different standard to other treatments

The list price as published is just over £500,000 per year per patient. This is comparable with similar enzyme replacement drugs currently in use by NHSE. Whilst the following numbers are approximate, they demonstrate that Brineura is not outside the 'norm' for such a treatment: Vimizim £400,000 per year, Elaprase £500,000 per year, Myozyme £500,000, and PEG-ADA £450,000 per year. It is unreasonable for NICE to apply a different standard to children with CLN2 Batten disease than they do to people with other rare diseases.

In addition to the grounds for appeal outlined above, the BDFA would like to raise concerns about the phrasing of section 4.30, which states: *"…disutility may change as siblings grow up and move on."* The severity of Batten disease is such that it has a huge impact on the whole family, including siblings, that the use of the phrase 'moving on' demonstrates a lack of understanding of the disease that undermines the decision-making process. Siblings of children with Batten disease are always siblings whether the child has died or is alive, and, of course have on-going issues around their reproductive choices irrespective of whether or not they are carriers.

Conclusion

There is clear agreement that cerliponase alfa benefits the children with CLN2 Batten disease and their families. There is a great number of countries that are offering access to the treatment. As the Batten disease community is a small one, our parents know all the clinicians and researchers who have been involved in obtaining treatment in their countries. In a community where parents face a journey that is brutal and devastating, our parents now face uncertainty and additional anxiety, because their health system places a lower value on their children.

Please let us know if you would like any clarification.

Yours sincerely

[redacted] [redacted]

Chair of Trustees Chief Executive