NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

sent by email: [redacted]; [redacted]

[redacted], Chair of Trustees
[redacted], Chief Executive
Batten Disease Family Association
209-211 City Road
London
EC1V 1JN

18 March 2019

Dear [redacted] and [redacted]

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

Thank you for your letter of 8 March addressed to Dr Benneyworth, lodging the Batten Disease Family Association's (BDFA) appeal against the above Final Evaluation Determination. I have taken over from Dr Benneyworth in overseeing NICE's appeal process.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly, or
- 1(b) NICE has exceeded powers;
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View:

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.

As the FED notes, NICE's published procedures state that benefits realised outside the health care system are not included in NICE's reference case. Those procedures have been consulted on and this approach applies to all appraisals, which helps to ensure a level playing field. It seems to me that the committee have followed NICE's rules, the result of which is that evidence of wider health related benefits is not relevant to the committee's decision, and so must not be taken into account.

I would not presently be minded to treat this as a valid appeal ground.

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.

As you will be aware, NICE has adopted the HST process so as to be able to consider treatments for rare diseases differently from treatments for less rare diseases. The HST process is more flexible than the standard TA process. I do not think it can be argued that the HST disadvantages rare disease patients relative to the alternatives, which would either be a standard HTA or no appraisal at all.

I think this appeal point is a general challenge to NICE's whole approach to evaluating treatments for rare conditions rather than a challenge to an unfairness specifically in this case, and so it would not be a valid appeal point.

I would not currently be minded to refer this appeal point to an appeal panel.

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

In the HST it is the manufacturer who puts together the evidence base for a treatment rather than NICE carrying out an investigation. The experience of families living with CLN2 was considered in the responses to consultation, and FED 4.37 acknowledges the cost of the disease to families. I do not think that NICE were obliged as a matter of fairness themselves to carry out further investigations.

I would not presently be minded to treat this as a valid appeal ground.

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…" 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.

The UN convention of the rights of persons with disabilities would be international law and so not directly applicable to NICE, but there is an equivalent right in Article 2 of the European Convention on Human Rights which is directly applicable by virtue of the Human Rights Act. However the case law on this right has never established a positive right to medical treatment outside of a few very narrow exceptions not applicable here. NICE has considered Article 2 (and 3 and 8) of the ECHR in past appeals and has a settled position that those articles do not render an otherwise lawfully conducted appraisal unlawful.

Your second appeal point in effect references the public sector equality duty imposed by s.149 of the Equality Act 2010. That is a "due regard" duty to consider the issues set out in that section rather than an absolute duty to take certain steps. I would ask you to come back to me with any arguments that NICE has not considered the status of children with CLN2 as people with disabilities, of the need to advance equality of opportunity etc.

I would not currently be minded to treat these as valid grounds of appeal.

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. .... Therefore, they are at liberty to withdraw from this market at any time. This places an additional enormous pressure

on families. No evidence has been presented that guarantees continued access to treatment for those already receiving it, ...

As you will know the Helsinki declaration governs continuation of treatment of clinical trial participants, and the continuation of a compassionate use scheme depends on what was agreed between the scheme sponsor and the patients. The NHS cannot be bound to continue treatment initially funded by a trail sponsor or manufacturer as that amounts to allowing third parties to dictate public funding decisions. While I would very much hope that any pharmaceutical company would behave responsibly and ethically, I do not think the possibility that it might not could be a relevant factor for NICE. NICE is limited to guidance on NHS funded treatment, and has provided that any current NHS funded treatment should continue, which meets the NHS's ethical obligations.

I would not currently be minded to treat this as a valid ground of appeal.

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.

My understanding of the FED is that the uncertainty that long term data collection would address was not the reason the treatment was not recommended, which was that the ICERs were too high. I am afraid I do not see a connection between there being a possible long term data collection plan that would gather valuable data, and recommending a treatment as a level of cost effectiveness that is considered to be too high.

I would not currently be minded to treat this as a valid ground of appeal.

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, ...

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.

I am not sure that I understand this point, because the change that was made to QALY thresholds was a change that was favourable to the drug in this case. If so I cannot see that making the change during a clinical trial (which NICE did not conduct) would be unreasonable. Even if the change had been in the other direction I would not agree that NICE was bound not to change a threshold during a third party clinical trial, because clinical trials across the range of treatments that are being or will be appraised by NICE are always ongoing.

While I note your point about QALYs, and that their advantages and disadvantages are the subject of discussion in their literature, NICE has consistently used them as a tool in its decision making for many years, and no better approach has yet been suggested (certainly, I cannot see that they can plausibly be said to be so flawed that they cannot reasonably be used.)

I would not currently be minded to treat this as a valid ground of appeal.

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.

Where a measure (in this case an early diagnosis campaign) is proposed as a means to improve cost effectiveness, I cannot see that it can be argued that NICE cannot consider how easily the measure could be implemented.

I would not currently be minded to treat this as a valid ground of appeal.

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.

NICE considers cost efficacy rather than cost, so direct comparison of costs between different treatments is likely to be misleading. Further I think you are comparing list prices Vimizim is subject to a managed access agreement rather than the list price. I could not find NICE recommendations for the other treatments you refer to.

I would not currently be minded to treat this as a valid ground of appeal.

Please would you let me have any further observations you may have on the points that I am not minded to consider valid within the next ten working days, **no later than Monday 1 April**, and I will then finalise my decision on initial scrutiny.

Yours sincerely

Tim Irish
Vice Chair
National Institute for Health and Care Excellence