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Andy McKeon
Vice chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Margaret,

Re: Final Evaluation Determination – Sebelipase alfa for treating lysosomal acid lipase deficiency (LAL D).

The MPS Society would like to appeal against the Final Evaluation Determination for the above mentioned highly specialised technology on the following grounds:

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

a) failed to act fairly

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

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

1.1a. The committee have failed to understand the superiority of Sebelipase alfa, compared to other approved ERT treatments.

It was noted within the FED document (5.4; 5.6) that Sebelipase alfa is the first therapy to specifically target the underlying cause of LAL D and that clinical opinion was that this was a step change in managing the condition and that the results of the Enzyme Replacement Therapy (ERT) are compelling. Having spoken to paediatricians, and adult clinicians across the specialist centres, clinicians have commented that Sebelipase alfa appears superior to many other ERT's and is the most effective ERT treatment seen for many years, especially in the infant population. We believe that the committee have failed to truly understand or acknowledge the unique effect and positive outcomes of Sebelipase alfa, a lifesaving treatment for a fatal disease.

1.2a. The committee have failed to recognise the severity of the disease in the infant population.

Throughout the FED, the committee has referred to the infant form of LAL D as being a rapidly progressive condition but has not reflected on the high mortality / morbidity rates of patients before Seblelipase alfa. (mean age being 3.7 months Jones et al 2015). Nor has it recognised the lifesaving effect of the treatment. We feel that this is a deliberate attempt to not recognise the true treatment effects and potential high life years it could give to this patient population. If this was recognised NICE would be compelled to recommend this treatment which clearly they are reluctant to do based on its perceived high cost.

This is further augmented by the recent HST of another treatment for Hypophosphatasia, where NICE approved treatment in the perinatal and infant population, viewing the drug to be lifesaving. This is a population similar to LAL D, where death is likely to occur in the first 6 months. We therefore feel that the infant group for LAL D has been discriminated against and denied access to treatment purely based on cost, as the clinical expert view is that the severity and potential responses of both diseases to their treatment is the same.

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

2.1 The committee's statement relating to infants coming off treatment reflects their lack of understanding and compassion of a fatal disease.

In section 1.3; the committee commented that *"Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop"*

It would be inhumane and unethical to withdraw treatment from an infant or child that was responding, putting them at risk of inevitable disease regression and rapid death. This is especially so for the infants, where it has been clearly stated and documented that best supportive care today has still not improved quality of life and does not prevent early death.

Would this not be seen as passive euthanasia by the Department of Health in the UK? Especially when the medical view on withdrawing treatment is that this should only be done, if a patient's quality of life was so poor, that life would be worse for them than death. I think we would all agree that this is not the case for patients with LAL D!

2.2 The committee's statement relating to patient representation was untrue and inappropriate.

The committee made reference to the patient experts involved in the appraisal potentially being biased to the treated patient population (5.2). We would like to remind the committee of the following.

1) The HST process only allows 3 patient representatives to be involved in the appraisal.
2) One patient expert had lost a child due to no treatment available and now has a child living and developing within a normal developmental range due to being enrolled on the clinical trial and receiving Sebelipase alfa. Therefore, representing both the non-treated and treated population for the infant form of the disease.
3) The patient expert from the MPS Society was there to represent all patient views. Both the Society's representative and clinical experts have been transparent and honest in their views that not all patients would require or want to access the treatment if it was available. This was reflected in the starting / stopping criteria in the MAA.
4) Due to the low patient incidence in this disease group; no late onset patients were diagnosed between the clinical trial closing and the HST appraisal for Sebelipase alfa starting. However, two recently diagnosed patients and their families have since shared

their views on wanting access to treatment both in the media and in their responses to the ECD's.

2.3 We believe that the committee's reservations on the long term health benefits of Sebelipase alfa not being achieved and the benefits being highly uncertain, due to the limited data available (5.22); to be invalid and subjective.

For infants, the clinical trial has currently been running for six years with the UK having greater experience than any other country. The oldest surviving patient is 6 years old and is demonstrating good quality of life and development. There are now seven patients in England being treated who are equally showing, long term survival, improved outcomes and demonstrating a good quality of life and normal cognitive and physical development. In a recent presentation at the World Symposium (Feb 13 -16 2017); reported outcomes were shared on five infant patients who had survived beyond 3 years of age following treatment of Sebelipase alfa. Four out of the five children were attending a nursery or school, with reports of good development and social interaction.

This surely shows that the life survival and long term benefits for patients on Sebelipase alfa is both compelling and positive compared to the untreated patient population where the disease is fatal in infancy.

Clinical data for the late onset group also shows improved outcomes in liver function (92%) 11 out of 12 patients had an improved or stable Ishak fibrosis stage (Goodman et al 2016) and was referred to as compelling by clinicians. This has also been demonstrated in the patient experts submission where quality of life has been significantly improved and day to day living has gone back to near normal adult life. The remarkable results and outcomes seen in the late onset group in our view, supports access to early treatment for the clinically at risk patient. In respect of the committee's uncertainties regarding the life expectancy of the late onset patient population as commented in section 4.2, this was reported on in the MPS Society's response to the committee's first ECD, where we reported that [redacted] from Chicago stated during a presentation at the WORLD symposium on Lysosomal Storage Disorders (Feb –March 2016) that 'no untreated patients reviewed lived over the age of 58 years.

The clinical outcomes and life saving benefits seen in patient responses, in our view is transformational in efficacy and demonstrates that Sebelipase alfa has real world clinical benefit that is not seen in other ERT's approved and available within England.

A solution found in other less effective ERT's to gather enhanced clinical outcomes and quality of life data was in the adoption of the Managed Access Agreement (MAA); We would therefore argue that as a precedent has already been set for other less effective ERT's and where Sebelipase alfa has demonstrated its potential to reverse disease burden and in the case of infants be lifesaving, implementing an MAA for a period of time to capture this important data would be a positive step and the ethical thing to do.

Conclusion

The patient community would appeal to NICE's rational side to see the real world clinical benefit of Sebelipase alfa; a drug that was fast tracked through the EMA due to the high death rate in the infant population and the need for early patient access to an effective treatment. Despite this approval, NICE continues to ignore its life saving effects whilst approving less effective ERT's. NHS England prides itself on having a fair and just system and we acknowledge that part of this system is ensuring value for money and cost effectiveness, but how can this be true when less effective and expensive therapies are approved over a treatment that has shown lifesaving properties and disease reversal.

"Davis 1994 concluded "unless the child is in the process of dying, continued survival is always on balance a benefit to the child, so that if treatment is not burdensome it should always be given" (quoted by Sarah Elliston 2007; The best interests of the child in Healthcare)

The MPS Society and patient representatives would be willing to be heard at an oral or written appeal

Yours sincerely

Advocacy Support Team Manager