

Sent: 13 June, 2018 10:11 AM

To: 'hst@nice.org.uk' <hst@nice.org.uk>

Subject: Submission to NICE on proposal to decline funding for Velmanase alfa for treating alpha-mannosidosis [ID800]

Importance: High

To the National Institute for Health and Clinical Excellence

A submission on your evaluation consultation document on [Velmanase alfa for treating alpha-mannosidosis \[ID800\]](#)

This submission is from ISMRD, www.ismrd.org an international, though US-based, not-for-profit established in 1999 to advocate world-wide for the needs and interests of patients and families affected by alpha-mannosidosis and related diseases. A few years later, ISMRD changed its branding to show its focus on all 9 glycoprotein diseases, of which alpha-mannosidosis is one. We have a network of several hundred families across the globe, including in the UK, who are affected by this small number of very rare diseases.

Our submission addresses each of the core questions you ask in your consultation document:

1. Has all of the relevant evidence been taken into account?
2. Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
3. Are the provisional recommendations sound and a suitable basis for guidance on the use of velmanase alfa in the context of national commissioning by NHS England?
4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Question 1 – the relevant evidence.

We note that your evaluation committee met on 25 April this year and no doubt had its papers prepared earlier. Since that date there are 3 published papers from 2 different and respected peer-reviewed journals which contradict your committee's conclusions on the clinical evidence. These papers by Lund AM et al, Harmatz P et al, and Borgwardt L et al, are cited here with their key conclusions highlighted in italics.

<https://www.ncbi.nlm.nih.gov/m/pubmed/29725868/?i=2&from=/29846843/related>

Enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase): Novel global treatment response model and outcomes in patients with alpha-mannosidosis. Lund AM et al. J Inherit Metab Dis. 2018 May 3. doi: 10.1007/s10545-018-0175-2. [Epub ahead of print]

CONCLUSIONS: Patients treated with velmanase alfa experienced improvements in biochemical and functional measures that were maintained for up to 4 years. Long term follow-up is important and further supports the use of velmanase alfa as an effective and well-tolerated treatment for AM. Based on the currently available data set, no baseline characteristic can be predictive of treatment outcome. Early treatment during paediatric age showed better outcome in functional endpoints.

<https://www.ncbi.nlm.nih.gov/m/pubmed/29716835/?i=2&from=/29725868/related>

Enzyme replacement therapy with velmanase alfa (human recombinant alpha-mannosidase): Novel global treatment response model and outcomes in patients with alpha-mannosidosis. Harmatz P, et al.. Mol Genet Metab. 2018 Jun;124(2):152-160. doi: 10.1016/j.ymgme.2018.04.003. Epub 2018 Apr 18.

The responder analysis model demonstrates a clinically meaningful treatment effect with velmanase alfa and supports the early initiation and continued benefit of longer-term treatment of all patients with alpha-mannosidosis with this ERT.

<https://www.ncbi.nlm.nih.gov/m/pubmed/29846843/?i=3&from=/29725868/related>

Efficacy and safety of Velmanase alfa in the treatment of patients with alpha-mannosidosis: results from the core and extension phase analysis of a phase III multicentre, double-blind, randomised, placebo-controlled trial. Borgwardt L, et al. J Inher Metab Dis. 2018 May 30. doi: 10.1007/s10545-018-0185-0. [Epub ahead of print]

CONCLUSIONS: These findings support the utility of VA for the treatment of AM, with more evident benefit over time and when treatment is started in the paediatric age.

We submit that the review needs to ensure all up-to-date and relevant evidence is considered, including these articles referred to here, plus additional commentary made in the following responses to subsequent questions.

Question 2 – the interpretation of the evidence.

We offer these critiques of your interpretation of the evidence.

A – We note you had some multi-domain responder information available to you in your evaluation, and possibly other unpublished data too, but ISMRD submits that you have reached the wrong conclusions about the evidence of clinical effectiveness. We believe the analysis should be revisited in light of these new published papers since the time of the work on which your preliminary conclusions were reached. Note that the authors of the papers mentioned above are experts in lysosomal diseases, and experienced in assessing evidence from very small patient cohorts.

B – We submit that your emphasis on uncertainty of the clinical evidence, which you have proposed as a major influence on your conclusions, is inconsistent with the finding of the European Medicines Agency when it recommended marketing approval in January 2018. NICE has failed to recognise the prime role that the EMA has in determining safety and efficacy of medicines. Note the principles in EMA publication

http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf

- To protect public health and ensure the availability of high quality, safe and effective medicines for European citizens, all medicines must be authorised before they can be placed on the market in the EU.
- Once a marketing authorisation has been granted, decisions about price and reimbursement take place at the level of each Member State considering the potential role and use of the medicine in the context of the national health system of that country.

C – Note also the EU's acceptance of that point when it granted marketing authorisation valid throughout the EU on 23 March 2018. Note the [statement from the EMA](#) on 26 January when announcing its recommendation to the EU:

“A marketing authorisation under exceptional circumstances allows patients access to medicines that cannot be approved using a standard authorisation route as comprehensive data cannot be obtained, either because there are only very few patients with the disease, the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge.”

This statement and the policy basis for it, give a “pass mark” to the clinical evidence, despite its limitations, and effectively declares the evidence sufficient. NICE should not be revising that point by attempting to relitigate the conclusions of the EMA regarding clinical evidence.

D – We do accept that the evidence points to legitimate concern about the cost of the treatment. But concerns about that should not be conflated nor confused with issues relating to the clinical evidence.

Question 3 – the soundness and suitability of the provisional recommendations.

Given the point made above, ISMRD submits that a more appropriate recommendation would conclude: **That there is sufficient evidence of benefit, but the product is not considered cost-effective to warrant a positive recommendation.**

The recommendation should then continue that:

Approval would be considered when negotiations with the company reach a suitable price agreement, and that further negotiation should be initiated.

We are aware of similar recommendations you have made in the recent past, and this should be done again in this case.

Question 4 – Avoiding unlawful discrimination.

There are general and specific comments we wish to make about discrimination.

A – General statements about the human rights dimension to this case.

It is disappointing that your evaluation has not included more discussion of legal and ethical principles. There are various high-level international instruments that, among other points, provide a right to health, promote universal healthcare, give a right to the highest attainable standard of health, and protect the rights of the child. All these instruments offer significant guidance about how decision making should adopt a wider perspective and more generous interpretation for those who are disadvantaged. The EU itself pursues a strong human rights framework within its rules and policies and endorses in practical ways many ethical principles such as distributive justice in the allocation of healthcare resources. The Orphan Drugs regulations, the EMA’s policies, and the EMA’s statement about the granting of marketing authorisation, are precise ways in which these principles are given effect. In not recommending velmanase alfa for treatment of patients with alpha-mannosidosis, NICE is clearly giving scant regard to the important human rights and ethical dimensions at stake here. Patients should not be abandoned by the health system when an effective intervention becomes available. Note also the statement made by Helen Clark, former head of the UN Development Programme, to the ICORD www.icord.se conference in 2016: “No country can claim to have achieved universal healthcare if it has not adequately and equitably provided for the needs of those with rare diseases”.

B – More specific points about human rights in this case.

- Patients with alpha-mannosidosis are always disabled by their disease. Some perhaps moderately, but most are disabled significantly, and some very severely.
- The Orphan Drug policies of the EU and the EMA are a specific attempt to redress the imbalance, and thus the inherent discrimination, that occurs when the needs of those with rare diseases are evaluated in a framework of equality with other diseases, regarding clinical evidence and cost-effectiveness. This is done by introducing equity into the mix, such as in the EMA's recommendation quoted above.
- In failing to maintain the rebalancing or equity theme adopted by the EMA and EU in granting marketing authorisation for velmanase alfa for patients with alpha-mannosidosis, NICE is effectively reintroducing discrimination into the equation for this significantly disadvantaged group of people who experience major disability, when it conducts its part of the decision process.
- We do not consider it acceptable nor consistent with human rights norms and legislation, for NICE to "undo" the affirmative action put in place within the EU in the long process of basic research into this disease, development and trials of the treatment, right up to the initial stages of registration and marketing approvals.

ISMRD submits that the failure of NICE to adapt its policy and procedures to specifically include equity as an overt expression of a human rights approach, as guided by the EU and the EMA, produces a result that is highly discriminatory to patients with alpha-mannosidosis. Because of their rarity they are subjected to significant disadvantage in your evaluation process, in ways that would not apply to much larger patient groups where disease knowledge, clinical evidence, economies of scale, more robust trial data, and various other factors, are much more easily determined.

Please reconsider your proposed recommendation in light of points we have raised in this submission.
Yours sincerely,

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