NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technology Evaluation

Recombinant human alpha-mannosidase for treating alpha-mannosidosis

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of recombinant human alpha-mannosidase within its licensed indication for treating alpha-mannosidosis for national commissioning by NHS England.

Background

Alpha-mannosidosis is a rare genetic disease caused by the deficiency of an enzyme called alpha-mannosidase. It is inherited as an autosomal recessive disorder, which means that both chromosome copies carry mutations in the alpha-mannosidase gene MAN2B1, and both parents may be unaffected carriers. Alpha-mannosidase breaks down oligosaccharides and in the absence of this, oligosaccharides accumulate inside cells, resulting in damage of tissues and organs and leading to cell death. This is characterised by skeletal changes, deterioration of bones and joints, muscle weakness, hearing loss, recurring infections and developmental impairment.

Alpha-mannosidosis can present at infancy, childhood or early adolescence. It can be severe, moderate or mild in its progression. The severe phenotype of alpha-mannosidosis manifests during infancy and is typically characterised by enlargement of the liver and severe infections and is associated with poor survival rates. Moderate disease is associated with slow progression but the characteristics of alpha-mannosidosis are evident and have a substantial impact on physical and mental wellbeing. These characteristics may be absent in people with mild disease.[1]

The exact prevalence is not known. According to published sources it is approximately 1 in 500,000[2] or 1,000,000.[1] Approximately 14 patients are thought to have been diagnosed with alpha-mannosidosis in the UK since 1961.

Allogeneic haematopoietic stem cell transplant (HSCT) from a family member or unrelated donor is a treatment option for patients with severe disease although there are significant risks associated with allogeneic HSCT. There are currently no pharmacological treatments for alpha-mannosidosis. Treatment options are aimed at managing symptoms, delaying progression and improving quality of life.

The technology

Recombinant human alpha-mannosidase (Lamazym, Chiesi) is a long-term enzyme replacement therapy for people with genetically determined alpha-mannosidosis. It is administered by intravenous infusion.

Recombinant human alpha-mannosidase does not currently have a marketing authorisation in the UK for alpha-mannosidosis. It has been studied in clinical trials in people with a confirmed diagnosis of alpha-mannosidosis as defined by alpha-mannosidase activity, that is, less than 10% of normal activity compared with placebo.

Intervention(s)	Recombinant human alpha-mannosidase
Population(s)	People with alpha-mannosidosis
Comparators	• Standard treatment without alpha-mannosidosis For people with severe disease • Allogeneic haematopoietic stem cell transplant
Outcomes	The outcome measures to be considered include: • reduction in oligosaccharides in blood serum • changes in alpha-mannosidosis disease clinical measures (for example lung function and biomarkers of disease severity) • motor and language function • 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 alpha-mannosidosis confirmed?

How is alpha-mannosidosis disease severity defined and categorised?

How many patients with alpha-mannosidosis are expected to be treated in NHS specialists centres annually?

Alpha-mannosidase has been studied in patients between the ages of 5 and 35 years.

- Would alpha-mannosidase be expected to be used in children younger than 5 years?

Are the comparators for alpha-mannosidase defined appropriately in the scope?

What is considered standard treatment without alpha-mannosidase in the NHS?

Describe which patients with alpha-mannosidosis would be considered for allogeneic haematopoietic stem cell transplantation?

Are there any subgroups of people in whom alpha-mannosidase 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 alpha-mannosidase 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.

References

1. Beck, M. et al. (2013). Natural history of alpha mannosidosis a longitudinal study. Orphanet Journal of Rare Disease 8:88.

2. Malm, D. (2008). Alpha-mannosidosis. Orphanet Journal of Rare Disease 3:21.