NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of Highly Specialised technologies guidance 3)

Draft scope

Remit/evaluation objective

To evaluate the benefits and costs of ataluren within its marketing authorisation for treating Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene for national commissioning by NHS England.

Background

Muscular dystrophies are a group of genetic disorders which cause muscle weakness and progressive disability. Duchenne muscular dystrophy is the most common and progresses most rapidly. It is caused by the presence of different types of mutations on the X-chromosome in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. The main types of mutation are deletions (where part of the gene is deleted), insertions (where an additional piece of DNA is inserted into the gene), duplications (when part of the gene is repeated) and point mutations (when a single letter in the DNA code is changed and alters the information needed to produce a protein). A point mutation that leads to a stop signal being inserted into the middle of a gene, that stops the protein being produced, is known as nonsense mutation. These changes cause muscle fragility that progressively leads to weakness and loss of walking ability during childhood and adolescence. Boys only have one X chromosome, and thus one single copy of the dystrophin gene, hence they have a much higher probability of developing Duchenne muscular dystrophy than girls. A very small number of girls develop Duchenne muscular dystrophy.

Initial symptoms of Duchenne muscular dystrophy usually present between the ages of 1 and 3 years and children with the disease may appear weaker than other children, and have difficulty walking, standing, or climbing stairs, and may have behavioural or learning difficulties. After the age of 12 most children will need to use a wheelchair. During adolescence, breathing muscles can weaken, causing shallow breathing and a less effective cough mechanism, which can lead to chest infections. Weakness of the heart muscle, called cardiomyopathy, occurs in almost all patients by the age of 18 years. The life expectancy of people with Duchenne muscular dystrophy depends on how quickly and intensely muscle weakness progresses and how it affects the patient's ability to breathe. The average lifespan is less than 30 years.

The prevalence of Duchenne muscular dystrophy is approximately 8.29 in 100,000.[1] Approximately 10% of patients with Duchenne muscular dystrophy carry a nonsense mutation in the dystrophin gene, equating to around 225 males aged over 2 years in England using current population size estimates.[2,3] The proportion of these people who are able to walk is unknown.

Increasing the time a patient is able to walk is one of the major aims of treatment. Treatment options for the management of Duchenne muscular dystrophy without ataluren do not treat the underlying cause of the disease and focus on alleviating symptoms and maintaining muscle strength. Interventions may include the use of steroids (associated with several side effects) and physical aids (such as wheelchairs, leg braces or crutches), exercise, physiotherapy, and occasionally orthopaedic surgery. In addition, other supportive treatments such as dietetic advice, prevention and treatment of bone fragility and the management of complications of long-term steroid therapy are required. In the later stages of Duchenne muscular dystrophy, treatments to help improve breathing and increase oxygen levels may be needed if lung function becomes impaired.

This evaluation is a review of NICE highly specialised technologies guidance on ataluren for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people aged 5 years and older who can walk (HST3), in line with the completion of the managed access agreement. Since Highly Specialised Technologies guidance 3, the conditional marketing authorisation for ataluren has been extended to include people between the ages of 2 and 5 years.

The technology

Ataluren (Translarna, PTC Therapeutics) is designed to allow the protein-making apparatus in cells to skip over the nonsense mutation, allowing the cells to produce a full length functional dystrophin protein. It is administered orally.

Ataluren has a conditional marketing authorisation in the UK for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. As part of the conditional marketing authorisation, the company will be required to provide data on the effectiveness and safety of ataluren from an ongoing confirmatory study.

Intervention(s)	Ataluren
Population(s)	People aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk
Comparators	Established clinical management without ataluren

Outcomes	The outcome measures to be considered include: • walking ability (ambulation) • muscle function • muscle strength • ability to undertake activities of daily living • cardiac function • lung function • time to wheelchair • number of falls • mortality • adverse effects of treatment • 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
Clinical Effectiveness	• 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 (if relevant)
Value for money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• 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 • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation
Related NICE recommendations and NICE Pathways	Related Highly Specialised Technologies Evaluations: 'Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene' (2016). NICE Highly Specialised Technologies Guidance 3. Review date March 2020. Appraisals in development (including suspended appraisals): 'Idebenone for treating Duchenne muscular dystrophy' NICE technology appraisal guidance [ID1092]. Publication date to be confirmed. 'Drisapersen for the first-line treatment of Duchenne's muscular dystrophy' NICE highly specialised technology guidance [ID911]. Publication date to be confirmed. 'Eteplirsen for treating Duchenne muscular dystrophy' NICE highly specialised technology guidance [ID1003]. Publication date to be confirmed.
Related national policy	Related NHS England policies: NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48 The NHS Long Term Plan, 2019. The NHS long term plan NHS England (2013) 2013/14 NHS standard contract for diagnostic service for rare neuromuscular disorders (all ages)

	Other related policies: Department of Health & Social Care (2019) The UK strategy for rare diseases: 2019 update to the Implementation Plan for England UK Rare Disease Forum (2016) Delivering for patients with rare diseases: Implementing a strategy A report from the UK Rare Disease Forum Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, 3, 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for ataluren been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for Duchenne muscular dystrophy resulting from a nonsense mutation?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

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 ataluren 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)?

References

1. Norwood FL et al. (2009) Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain: 132(11); 3175-3186

2. Bladen CL et al. (2015) The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Human Mutation: 36(4); 395–402

3 Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2018. Accessed March 2020.