NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technology Evaluation

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

Draft scope (Pre-referral)

Draft 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 certain defects (called nonsense mutations) on the X-chromosome in the gene for dystrophin, a protein that is important for maintaining normal muscle structure and function. The mutation prematurely stops the production of a normal dystrophin protein, leading to a shortened dystrophin protein that does not function properly. 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 if they inherit two mutated X-chromosomes, one from each of their parents.

Duchenne muscular dystrophy usually presents between the ages of 1 and 3 years and affected children 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 18. The life expectancy of people with Duchenne muscular dystrophy depends on how quickly and intensely muscle weakness progresses and on how it affects the patient's ability to breathe. The average lifespan is less than 30 years.

The incidence of Duchenne muscular dystrophy is approximately 1 in 5000 male live births. Approximately 13% of patients with Duchenne muscular

dystrophy carry a nonsense mutation in the dystrophin gene, equating to around 10 boys born with the condition each year in the UK.

Increasing the time a patient is able to walk is one of the major aims of treatment. Current treatment options tend to focus on alleviating symptoms and maintaining muscle strength. Interventions may include the use of steroids 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.

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 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 5 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. It has been studied in clinical trials compared with placebo in boys aged 7 years and older with Duchenne muscular dystrophy caused by a nonsense point mutation in the dystrophin gene who could walk at least 75 metres during a 6-minute walk test.

Intervention(s)	Ataluren
Population(s)	People aged 5 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 • mortality • adverse effects of treatment • health-related quality of life.
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 (if relevant)
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 or the CE marking if it is a device. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	None
Related National Policy	Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48 http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for treating Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene?

How is Duchenne muscular dystrophy with nonsense mutation in the dystrophin gene diagnosed in the NHS?

The marketing authorisation is limited to ambulatory patients. How is this population defined in clinical practice? How will this specification be adhered to in clinical practice?

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

Please describe any existing services in England for the diagnosis and management of this condition.

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)?

NICE intends to appraise 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 evluation processes is available at http://www.nice.org.uk/media/DE4/9A/HSTCombinedInterimProcessMethods.pdf.)