NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eteplirsen for treating Duchenne muscular dystrophy

Final scope

Remit

To evaluate the benefits and costs of eteplirsen within its licensed indication for treating Duchenne muscular dystrophy 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 one of the most common and severe forms. 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, and which is missing in people with Duchenne. 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 individual letters in the DNA code are changed, altering the information needed to produce a protein). These mutations cause muscle fragility that progressively leads to weakness and loss of walking ability during childhood and adolescence. About 60% of Duchenne muscular dystrophy is due to deletions within the dystrophin gene. In this case, part of the gene is deleted and a technique called splicing can be used to restore a functional genetic code. The genetic code for dystrophin is dispersed over exons. Exons are connected by introns, which do not contain the functional genetic code. When a part of the gene is deleted, splicing is a process that removes introns so that the protein translation between exons can be maintained.

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. 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 29 years.

The incidence of Duchenne muscular dystrophy is approximately 1 in 3500–6000 male live births.[1] Approximately 11–13% of people with Duchenne muscular dystrophy [2,3] is expected to have deletions that are amenable to treatment with exon 51 skipping and therefore would be eligible for eteplirsen.

In the ambulant population (people who are able to walk), increasing the time a patient is able to walk is one of the major aims of treatment. In the non-ambulant population delaying the loss of further muscle function is one of the major aims of treatment. Current treatment options do not treat the underlying cause of the disease and focus on alleviating symptoms and maintaining muscle strength. Interventions may include the use of corticosteroids (associated with several side effects), vitamin D supplementation and physical aids (such as wheelchairs, leg braces or crutches), 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, cardiac management and treatments to help improve breathing and increase oxygen levels may be needed if lung function becomes impaired.

The technology

Eteplirsen (brand name unknown, Sarepta Therapeutics) is a phosphorodiamidate morpholino oligomer and is designed to skip an exon (exon 51) of the dystrophin gene to correct the reading frame of dystrophin transcripts for the synthesis of a shorter but functional dystrophin protein. It is administered by intravenous infusion.

Eteplirsen does not currently have a marketing authorisation in the UK for treating Duchenne muscular dystrophy. It has been studied in clinical trials in ambulant males aged 7 years and older who have Duchenne muscular dystrophy resulting from a mutation that was correctable by exon 51 skipping.

Intervention(s)	Eteplirsen with established clinical management
Population(s)	People with Duchenne muscular dystrophy that is amenable to treatment with exon 51 skipping
Comparators	Established clinical management without eteplirsen
Outcomes	The outcome measures to be considered include: • walking ability (ambulation) (for example 6 minute walk test and North Star Ambulatory Assessment) • muscle function

	• muscle strength (upper and lower limbs) (for example ability to rise independently) • ability to undertake activities of daily living (for example eating and using computers) • cardiac function • lung function (for example lung capacity, time to assistive ventilation, and ability to cough) • time to loss of ambulation • number of falls • time to scoliosis • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• extent of 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	• 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, and on the delivery of the	• whether there are significant non-health benefits • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the

specialised services	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 • additional staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. The use of eteplirsen is conditional on the presence of mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping. The economic modelling should include the costs associated with diagnostic testing for mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping in people with Duchenne muscular dystrophy who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.
Related NICE recommendations and NICE Pathways	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (July 2016) NICE Highly Specialised Technologies guidance 3. To be reviewed in 2020. Quality Standard in development: Neurological problems (relatively uncommon neurological problems e.g. muscular dystrophy). Status: Referred. Earliest anticipated date of publication: to be confirmed. Suspended Highly Specialised Technologies evaluation (marketing authorisation withdrawn): Drisapersen for the first-line treatment of Duchenne's muscular dystrophy [ID911].
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 Specialist neuroscience services for children and young people – chapter 119 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 Diagnosis and management of Duchenne muscular dystrophy, Duchenne Muscular Dystrophy Care Considerations Working Group, 2011 (NICE Accredited) http://www.nice.org.uk/Media/Default/About/accreditation/accreditation-decisions/Duchenne-Muscular-Dystrophy-Care-Considerations-Working-Group-final-decision.pdf

References

1 Mah JK, et al. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscul Disord. 2014;24:482–91.

2 Kinali M, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. Lancet Neurol. 2009;8:918–928.

3 Aartsma-Rus A, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. Hum Mut. 2009;30:293–299. doi: 10.1002/humu.20918.