# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Proposed Highly Specialised Technology Evaluation

## Drisapersen for treating Duchenne muscular dystrophy

## Draft scope (pre-referral)

### Draft remit/evaluation objective

To evaluate the benefits and costs of drisapersen 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 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 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 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 3600–6000 male live births.

Increasing the time a patient is able to walk 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), creatine supplementation 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

Drisapersen (brand name unknown, BioMarin EUMEA) is a 2'-O-methyl antisense oligonucleotide 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 functional dystrophin protein. It is administered by subcutaneous injection.

Drisapersen does not currently have a marketing authorisation in the UK for treating Duchenne muscular dystrophy. It has been studied in one randomised, placebo-controlled trial in ambulant males aged 5 years and older who had Duchenne muscular dystrophy resulting from a mutation that was correctable by exon 51 skipping.

| | |
|---|---|
| **Intervention** | Drisapersen |
| **Population** | People with Duchenne muscular dystrophy that is amenable to treatment with exon 51 skipping |
| **Comparator** | Established clinical management without drisapersen |
| **Outcomes** | The outcome measures to be considered include:<br>• walking ability (ambulation)<br>• muscle function<br>• muscle strength<br>• ability to undertake activities of daily living<br>• cardiac function |

| | |
|---|---|
| | • lung function<br>• time to wheelchair<br>• number of falls<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers). |
| **Nature of the condition** | • disease morbidity and patient clinical disability with current standard of care<br>• impact of the disease on carer's quality of life<br>• extent and nature of current treatment options |
| **Impact of the new technology** | • clinical effectiveness of the technology<br>• overall magnitude of health benefits to patients and, when relevant, carers<br>• heterogeneity of health benefits within the population<br>• robustness of the current evidence and the contribution the guidance might make to strengthen it<br>• 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)<br>• robustness of costing and budget impact information<br>• technical efficiency (the incremental benefit of the new technology compared to current treatment)<br>• productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used)<br>• 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** | • whether there are significant benefits other than health<br>• whether a substantial proportion of the costs (savings) or benefits are incurred outside of the |

| | |
|---|---|
| **delivery of the specialised services** | NHS and personal and social services<br>• the potential for long-term benefits to the NHS of research and innovation<br>• staffing and infrastructure requirements, including training and planning for expertise. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation.<br>The use of drisapersen 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** | Related Technology Appraisals:<br>HST Technology Appraisal in Preparation, 'Duchenne muscular dystrophy (nonsense mutation) – ataluren' ID428, Earliest anticipated date of publication February 2016<br><br>Related Guidelines:<br>Quality Standard Guideline in Preparation, 'Neurological problems (relatively uncommon neurological problems e.g. muscular dystrophy)' Status: Referred. Earliest anticipated date of publication: TBC |
| **Related National Policy** | Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48<br>http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf<br>Specialist neuroscience services for children and young people – chapter 119<br>http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf<br>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<br><br>Diagnosis and management of Duchenne muscular dystrophy, Duchenne Muscular Dystrophy Care Considerations Working Group, 2011 (NICE Accredited)<br><br>http://www.nice.org.uk/Media/Default/About/accreditation/accreditation-decisions/Duchenne-Muscular-Dystrophy-Care-Considerations-Working-Group-final-decision.pdf |

**Questions for consultation**

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

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

The clinical trial was conducted in males aged 5 years and older with Duchenne muscular dystrophy resulting from a mutation correctable by exon 51 skipping? How this type of mutation currently tested in the NHS? Are validated tests readily available? Is it tested routinely in current clinical practice?

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

Are there any subgroups of people in whom drisapersen 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 drisapersen will be 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.