# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Proposed Health Technology Appraisal

## Idebenone for treating Duchenne muscular dystrophy

## Draft scope (pre-referral)

### Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of idebenone within its marketing authorisation for treating Duchenne muscular dystrophy.

### 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 lack of dystrophin 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. 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 rate of Duchenne muscular dystrophy was between 10.7 to 27.8 per 100,000 live born males.[1] About 100 boys are born with Duchenne muscular dystrophy each year, and there are about 2,500 boys living with the condition in the UK at any one time.[2]

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. NICE highly specialised technology evaluation 3 recommended ataluren for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. In the non-ambulant population delaying the loss of further muscle function is one of the major aims of treatment. Importantly, lung and cardiac function can become impaired in later stages of Duchenne muscular dystrophy. Current respiratory support focusses on alleviating symptoms and improving breathing and can include assistive ventilation, non-invasive ventilation, cough assist machines and physiotherapy. Respiratory status also impacts the feasibility of orthopaedic surgery and is a major cause of morbidity and mortality. Idebenone is aimed at delaying respiratory decline in patients with Duchenne muscular dystrophy, irrespective of mutation status and ambulation.

More broadly, interventions focussing on alleviating symptoms and maintaining muscle strength 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.

### The technology

Idebenone (Raxone, Santhera Pharmaceuticals) is a synthetic short-chain benzoquinone analogue of co-enzyme Q10, a component of the respiratory chain. It aims to improve mitochondrial respiratory chain function, and is an antioxidant. It is administered orally.

Idebenone does not currently have a marketing authorisation in the UK for treating Duchenne muscular dystrophy. It has been studied in clinical trials compared with placebo in people with Duchenne muscular dystrophy aged between 8 and 18 years. A key trial included patients with declined respiratory function (that is, percent predicted peak expiratory flow ≤ 80%), and who were not taking concomitant corticosteroids.

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| **Intervention(s)** | Idebenone |
| **Population(s)** | Patients with Duchenne muscular dystrophy in whom respiratory function has started to decline and who are not taking concomitant glucocorticoids. |
| **Comparators** | Established clinical management without idebenone |

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| **Outcomes** | The outcome measures to be considered include:<br>• pulmonary function (for example respiratory function parameters including lung capacity, time to assistive ventilation, and ability to cough)<br>• cardiac function<br>• walking ability (for example walk test and North Star Ambulatory Assessment)<br>• motor function<br>• muscle strength (for example ability to rise independently or hand-held myometry)<br>• time to scoliosis<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers). |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation.<br>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 and NICE Pathways** | Related Technology Appraisals:<br>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.<br><br>Suspended appraisals<br>Drisapersen for the first-line treatment of Duchenne's |

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| | muscular dystrophy [ID911]. Suspended Highly Specialised Technologies evaluation (marketing authorisation withdrawn).<br><br>Proposed appraisals<br><br>Eteplirsen for treating Duchenne muscular dystrophy [ID1009] Proposed NICE technology appraisal Publication date to be confirmed.<br><br>Quality Standard in development:<br><br>Neurological problems (relatively uncommon neurological problems e.g. muscular dystrophy). Status: Referred. Earliest anticipated date of publication: to be confirmed.<br><br>http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp<br><br>Related NICE Pathways:<br><br>Duchenne muscular dystrophy (2016) NICE pathway<br><br>http://pathways.nice.org.uk/ |
| **Related National Policy** | Diagnostic service for rare neuromuscular disorders (adults and children) – chapter 48<br><br>http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf<br><br>Manual for Prescribed Specialised Services 2016/2017. Chapter 119. Specialist neuroscience services for children and Chapter 11. Adult specialist neurosciences services. NHS England, May 2016.<br><br>https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf<br><br>NHS Outcomes Framework 2016 to 2017. Department of Health, April 2016.<br>https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017<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/accreditatio |

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| | n/accreditation-decisions/Duchenne-Muscular-Dystrophy-Care-Considerations-Working-Group-final-decision.pdf |

## Questions for consultation

What is established clinical management without idebenone likely to include?

Would idebenone be used alongside corticosteroids?

Would idebenone be used only in patients with a decline in respiratory function and, if yes, how would this be defined?

Are the outcomes listed appropriate? Have all relevant outcomes been included in the scope?

Are there any subgroups of people in whom idebenone is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider idebenone will fit into the existing NICE pathway, Duchenne muscular dystrophy? 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 idebenone 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 Committee to identify and consider such impacts.

Do you consider idebenone 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)?

Do you consider that the use of idebenone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

**References**

1 Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. (2014) A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscular Disorders. 24(6):482-91.

2 NHS choices. Muscular dystrophy. Accessed November 2016. http://www.nhs.uk/conditions/Muscular-dystrophy/Pages/Introduction.aspx

3 Muscular Dystrophy UK. Duchenne muscular dystrophy. Accessed November 2016. http://www.musculardystrophyuk.org/app/uploads/2015/05/DMD-factsheet.pdf