Idebenone (Raxone) for Duchenne muscular dystrophy – first line

LAY SUMMARY

Duchenne muscular dystrophy is an inherited condition that mainly affects boys and causes muscle weakness. Most people with Duchenne muscular dystrophy are diagnosed by the age of 5 years, and need to use a wheelchair by the age of 12 years. Many will face severe health problems by their late teens as their heart muscle and chest muscles become weaker, eventually affecting their breathing.

Idebenone is a new drug for the treatment of Duchenne muscular dystrophy given as a tablet three times a day. It is being studied to see how well it slows down the weakening of breathing and heart muscles, and to see if it is safe for patients to take.

If idebenone is licensed for use in the UK, it could be a new treatment option for patients with Duchenne muscular dystrophy and may reduce symptoms of the disease and improve survival. At the moment, there are no drugs that treat the underlying cause of Duchenne muscular dystrophy.

NIHR HSRIC ID: 5162
TARGET GROUP

- Duchenne muscular dystrophy (DMD) – first line.

TECHNOLOGY

DESCRIPTION

Idebenone (Raxone; SNT-MC17) is a synthetic short-chain benzoquinone analogue of co-enzyme Q10 and a cofactor for the enzyme NAD(P)H:quinone oxidoreductase (NQO1). It improves mitochondrial respiratory chain function, and therefore energy production, by enhancing electron flux. Idebenone is also a potent antioxidant; this provides a strategy for the treatment of mitochondrial disorders characterised by excessive oxidative damage. In the phase III clinical trial, idebenone is administered orally at 900mg each day.

Idebenone (Raxone) is currently licensed in the EU for the treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy. In the phase III clinical trial, the most common reported adverse events were nasopharyngitis (25.8%) and headaches (19.7%). Idebenone is also in phase II clinical development for the treatment of primary progressive multiple sclerosis.

INNOVATION and/or ADVANTAGES

If licensed, idebenone will offer an additional treatment option for patients with DMD who currently have few effective therapies available.

DEVELOPER

Santhera Pharmaceuticals Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Idebenone is a designated orphan drug in the EU and USA and currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

DMD is the most common and severe type of muscular dystrophy, a broad class of more than 30 rare, incurable genetic disorders. DMD is inherited in an X-linked recessive fashion, and therefore almost exclusively affects males. The disease occurs as a result of mutations in the dystrophin gene, which leads to absence of, or defects in the protein dystrophin. Dystrophin has a structural role in linking the muscle cytoskeleton to the extracellular matrix; it is also involved in cell signalling and regulating muscle response to oxidative stress. The reduction or absence of dystrophin in skeletal and cardiac muscle leads to costamere disorganisation, sarcolemma fragility, and mechanically induced muscle fibre degeneration.
DMD classically presents in male children by 5 years of age\(^8\), and progressive skeletal muscle weakness and degeneration results in the loss of ambulation between the ages of 7 and 13 years\(^6\). Death typically occurs in the second or third decade of life from cardiac or respiratory failure; though provision of respiratory support, with ventilator use at the appropriate stage, can prolong survival into the fourth decade\(^5\). In 90% of cases, death is the result of respiratory failure, while in the remaining 10% it is the result of cardiac involvement\(^9\). Several dystrophin isoforms are also expressed in the brain, and their deficiency is responsible for the learning difficulties which complicate the course of the disease in approximately one third of cases\(^7\).

**NHS or GOVERNMENT PRIORITY AREA**


**CLINICAL NEED and BURDEN OF DISEASE**

DMD primarily affects males with an estimated incidence of 1 in 3,500 live male births\(^3\). Females who are heterozygous for the defective DMD gene are usually asymptomatic but a small percentage of female carriers, approximately 8-10%\(^10\), manifest milder forms of the disease\(^11\). The Muscular Dystrophy Campaign estimates that there are approximately 100 boys born with DMD in the UK every year, and there are approximately 2,500 boys living with the condition in the UK at any one time\(^12,13\). In 2013-14, there were 965 admissions for muscular dystrophy (ICD -10 G71.0) in England, which includes DMD along with other muscular dystrophies, resulting in 2,296 bed days and 1,048 finished consultant episodes\(^14\).

Without intervention, the condition of those affected deteriorates rapidly; untreated boys become wheelchair bound by the age of 12 years and die of cardiorespiratory complications in their late teens to early 20's\(^15\). The use of assisted ventilation has increased the median survival of patients with DMD; however, the average lifespan is still less than 30 years\(^16,17\). In 2013 there were 128 deaths (93 men, 35 women) from muscular dystrophy registered in England and Wales (ICD-10 G71.0)\(^18\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

- Muscular Dystrophy Campaign. Duchenne Standards of Care. 2009\(^19\).
CURRENT TREATMENT OPTIONS

There is currently no cure available for DMD. Therefore treatments predominantly focus on the management of symptoms and secondary complications\(^3\). This requires an interdisciplinary approach involving physicians, therapists, counsellors, and other specialists to improve the life expectancy and quality of life of patients\(^5\). Glucocorticoids are the only pharmacological treatments that have been shown to improve skeletal muscle strength and function in reproducible randomised controlled trials\(^{15}\); they also reduce the risk of scoliosis, stabilise pulmonary function, and may also improve cardiac function\(^4\). Current guidelines recommend initiation of glucocorticoids (such as prednisolone or deflazacort) once patients reach a plateau of motor skill development, generally at age 4-6 years, but prior to onset of motor decline\(^{15}\). However, it is estimated that a quarter of patients with DMD are ineligible for corticosteroid treatment due to its significant adverse effect profile\(^3\).

Other pharmacologic therapies for DMD are primarily aimed at the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure\(^5\). These treatment options include\(^5\):
- Angiotensin-converting-enzyme (ACE) inhibitors.
- β blockers.
- Calcium and vitamin D supplements.
- Muscle relaxants.
- Non-steroidal anti-inflammatory drugs.

Surveillance of the respiratory, cardiac, orthopaedic, nutritional and general medical issues associated with DMD allows anticipation, early detection and treatment of these complications\(^{15}\).

Supportive care for DMD also includes\(^5\):
- Physical therapy.
- Occupational therapy.
- Orthopaedic surgery.
- Genetic counselling.
- Invasive and non-invasive ventilation.
- Implanted cardiac devices.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>DELOS, NCT01027884, SNT-III-003; idebenone vs placebo; phase III.</th>
<th>DELPHI, NCT00654784, SNT-II-001; idebenone vs placebo; phase II.</th>
<th>DELPHI Extension, NCT00758225, SNT-II-001-E; idebenone; phase II extension.</th>
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</thead>
<tbody>
<tr>
<td>Status</td>
<td>Published.</td>
<td>Published.</td>
<td>Published.</td>
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<tr>
<td>Source of information</td>
<td>Publication(^3), trial registry(^1), manufacturer.</td>
<td>Publication(^3), trial registry(^{21}), manufacturer.</td>
<td>Publication(^3), trial registry(^{22}), manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (not UK) and USA.</td>
<td>Belgium.</td>
<td>Belgium.</td>
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<td>Participants</td>
<td>n=64; aged 10-18 years; males; Duchenne muscular dystrophy; no symptomatic cardiomyopathy or heart failure; no previous use of</td>
<td>n=21; aged 8-16 years; males; Duchenne muscular dystrophy; presence of cardiac involvement/dysfunction;</td>
<td>n=19; aged 8-16 years; males; Duchenne muscular dystrophy; completion of study SNT-II-001 (NCT00654784).</td>
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<td>Schedule</td>
<td>Randomised to idebenone 300mg oral three times daily; or placebo oral three times daily.</td>
<td>Randomised to idebenone 150mg oral three times daily; or placebo oral three times daily.</td>
<td>Subjects ≤45kg receive idebenone oral at 150mg three times daily; subjects ≥45kg receive idebenone oral at 300mg three times daily.</td>
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<td>Follow-up</td>
<td>Active treatment for 1 year.</td>
<td>Active treatment for 1 year.</td>
<td>Active treatment for 2 years.</td>
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<td>Primary outcome/s</td>
<td>Relative change in PEF from baseline to week 52.</td>
<td>Relative change in peak systolic radial strain of left ventricle inferolateral wall from baseline to week 52.</td>
<td>Safety and tolerability of idebenone measured by the nature and frequency of adverse effects, blood and urine laboratory measures, physical examination, vital signs, and electrocardiogram.</td>
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<td>Secondary outcomes</td>
<td>Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), muscle strength and motor function, quality of life, and safety and tolerability.</td>
<td>FVC, FEV1, PEF, maximal inspiratory pressure (MIP), timed 10 metre walking test, skeletal muscle strength score, adverse events, blood and urine laboratory measures, and electrocardiogram.</td>
<td>PEF, MIP, FVC, motor function test, skeletal muscle strength score, hand-held myometry, echocardiography, and colour doppler myocardial imaging.</td>
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<td>Key results</td>
<td>For idebenone vs placebo group respectively: change in PEF as % of predicted relative to baseline at 52 weeks, 3.1% vs 9.0%; change in FEV1 as % of predicted relative to baseline at 52 weeks, 2.4% vs 10.7%; change in FVC as % of predicted relative to baseline at 52 weeks, 5.7% vs 9.0%.</td>
<td>For idebenone vs placebo group respectively: mean increase from baseline in peak systolic radial strain values, 17.3% vs 7.5%; mean increase in PEF over the predicted value, 2.8% vs 8.5%.</td>
<td>MIP remained stable. No significant decrease in PEF. Decline in FVC as % of predicted, 61.3% at baseline vs 48.8% at month 24.</td>
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<td>Adverse effects (AEs)</td>
<td>At least one AE was reported by 93.8% and 94.1% of idebenone and placebo-treated groups, respectively. The most common AEs were nasopharyngitis (25.8%) and headaches (19.7%). Serious AEs were reported by 6.3% of idebenone.</td>
<td>At least one AE was reported by 92.3% and 100% of idebenone and placebo-treated groups, respectively. The most common AEs were upper respiratory tract infection (55.8%), rhinitis (27.9%) and viral infections (27.9%). Serious AEs were AEs were reported by 89.5% of patients. The most commonly reported AEs were upper respiratory tract infection (42.1%) and gastrointestinal infection (26.3%). Eight patients experienced a serious AE, but in no cases did this lead to permanent study</td>
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<td>treated patients and 14.7% of placebo-treated patients.</td>
<td>reported by 7.7% of idebenone-treated patients and 12.5% of placebo-treated patients.</td>
<td>treatment discontinuation.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of idebenone is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ✓ Reduced mortality/increased length of survival
- □ Other.
- ✓ Reduced symptoms or disability
- □ No impact identified

**Impact on Health and Social Care Services**
- □ Increased use of existing services
- □ Re-organisation of existing services
- □ Other.
- ✓ Decreased use of existing services
- □ Need for new services
- □ None identified

**Impact on Costs and Other Resource Use**
- □ Increased drug treatment costs
- □ Other increase in costs.
- ✓ Other: unknown drug treatment costs.
- □ Reduced drug treatment costs
- □ Other reduction in costs.
- □ None identified

**Other Issues**
- □ Clinical uncertainty or other research question identified.
- ✓ None identified

**REFERENCES**


